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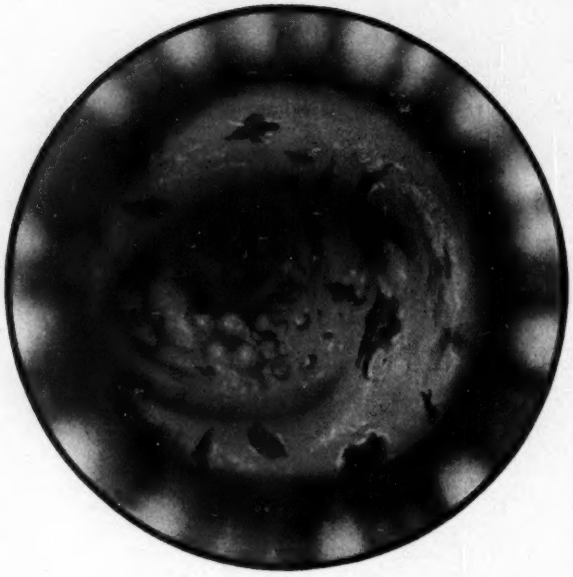

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1. Dowling, H. F., et al.: Ann. New York Acad. Sc. 53:433 (Sept. 15) 1950.

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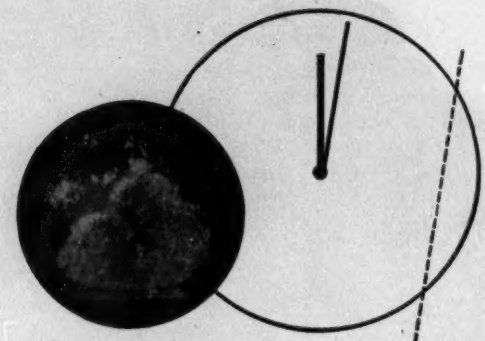

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(INCORPORATING THE AMERICAN JOURNAL OF GASTROENTEROLOGY)

The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

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The Review of Gastroenterology

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PROLAPSE OF THE GASTRIC MUCOSA THROUGH THE PYLORUS WITH CONCOMITANT GASTROINTESTINAL PATHOLOGY*

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During the past decade increasing attention has been directed by many authors[1-8] to the importance of prolapse of the gastric mucosa through the pylorus as a cause of a wide variety of clinical symptoms. The incidence of this condition has been reported as ranging from 0.19 per cent[2] to 7.7 per cent[9] on routine radiologic examinations of the stomach. Scott[1], however, failed to find a single instance of this phenomenon in any of 200 sailors who were free of gastrointestinal symptoms.

The symptomatology ascribed to herniation of the gastric mucosa into the duodenum has been indeed variable. Epigastric fullness, postprandial distress, nausea, vomiting, hemorrhage, and even carcinomatous degeneration[10] have been reported. While some authors[2] stress the discomfort produced by the ingestion of food, Wilson and Granger[6] report that all their cases with dyspepsia obtained relief from food. Although the symptomatology described has at times resembled that of peptic ulcer, Scott[1] emphasized the failure of alkalis to relieve the symptoms. Associated lesions of the gastrointestinal tract have been noted by Melamed[5], who also suggests that the gastric symptoms in cardiac failure may be the result of edema of the prepyloric mucosa with resultant prolapse into the duodenum. A similar finding was noted by the same author in a case of carcinoma of the esophagus. He postulated that lowered serum proteins due to malnutrition in such cases could result in edema of the antral mucosa with subsequent herniation through the pylorus.

The etiology of prolapsing gastric mucosa is still uncertain. Hypertrophic gastritis[11], pylorospasm followed by hyperperistalsis[2], and failure of the normal "stretching mechanism" of the mucous membrane during antral peristalsis[12] have been suggested as causative factors. The pathologic findings in resected specimens

*Read before the Fifteenth Annual Convention of the National Gastroenterological Association, New York, N. Y., 9, 10, 11 October 1950.

have been variable. The herniated mucosa was found to be normal in some cases[18] and the site of gastritis in others[13,14]. The pyloric ring was found to be contracted by Rees[2] while others have reported either a normal or wide pylorus[5,8,13].

It is our purpose in this communication to report our observations on the clinical significance of prolapse of the gastric mucosa through the pylorus when associated with other pathologic conditions of the gastrointestinal tract. The illustrative cases are patients who were x-rayed in the office of the senior author. Further reports will follow dealing with the incidence of this condition in an unselected

Fig. 1a—(Case 1) Prolapse of the gastric mucosa through the pylorus and duodenal diverticulum in a patient with an hiatus hernia. The latter is demonstrated in Fig. 1b. The patient's symptoms were related solely to the hernia.

series of 1,000 consecutive patients[15], with the failure of surgery to relieve symptoms in four patients[16], and with pathologic studies on the prepyloric mucosa[17].

Radiologic Criteria

Prolapse of the gastric mucosa is primarily a radiologic diagnosis. It is readily recognized under fluoroscopy and is more prominent if manual pressure is made from the antrum toward the pylorus during a peristaltic wave. Although this phenomenon involves only the mucosa, like intussusception elsewhere in the gastrointestinal tract, it is usually transient and hence may be present on only a single of many films taken of the pyloroduodenal region. It may be observed in all posi-

tions which define the base of the duodenal bulb, but is best demonstrated on films taken in the right lateral or right oblique prone positions.

Only a single fold may protrude through the pylorus and present a smooth polyp-like defect in the central portion of the base of the duodenal bulb (Fig. 11). In the large majority of cases, however, several folds or the entire circumference of the prepyloric mucosa passes through the pyloric ring and produces a mushroom or umbrella-shaped defect at the base of the bulb. The depressions between the prolapsed gastric rugae can frequently be recognized radiating outward from the central canal (Fig. 7). In a profile view of the bulb, the multiple defects may be seen corresponding to the prolapsed rugae (Fig. 10). However, at times, the protruding mucosa forms a collar and hence the defect is smooth and in these cases there is difficulty in differentiating it from the impression made by the pylorus on the base of the bulb (Fig. 9). This difficulty is accentuated if angular or basal projections of the duodenal bulb are obtained (Fig 6a).

Fig. 1b

Observations

Prolapse of the gastric mucosa through the pylorus is a common observation during the course of radiologic study of the pyloroduodenal region. The extent of mucosal prolapse is variable in the same patient even during the course of a single examination, hence no attempt is made to classify the degree of prolapse in this report. While the present discussion deals with its presence in association with other pathologic entities, it may be stated here that it occurs in individuals who have never had any gastrointestinal complaints as well as in those whose pathology is totally unrelated to the stomach or duodenum. Thus, it has been observed by us in association with every common disease of the stomach, duodenum, biliary tract, liver and the pancreas as well as in diseases of the lower intestinal canal.

It is somewhat more common in men than in women and its incidence is considerably higher in obese or hypersthenic individuals than in those who are normal or underweight.

Association With Diseases of the Stomach and Duodenum

a. *Hiatus Hernia:*—Extrusion of the antral mucosa through the pylorus has a relatively high incidence in patients with hiatus hernia.

Case 1 (Fig. 1a & 1b):—Male, age 42, with four year history of precordial and epigastric pain precipitated by consuming a large meal. Symptoms occurred chiefly at night and were relieved by sitting up and belching. There was some transient relief with alkaline powders, but no benefit was obtained by alumina gels. He had gained over 30 pounds during the past 5 years and was considerably overweight. His symptoms were aggravated when under emotional tension. Physical examination was negative apart from obesity and some tenderness below the xyphoid. Complete x-ray investigation revealed a reducible hiatus hernia, prolapse of the gastric mucosa through the pylorus and a duodenal diverticulum. Gastric analysis, gastroscopy and stool examination were normal. He was placed on a bland diet with trasentin and phenobarbital and instructed to sleep in a semi-recumbent position. Weight reduction was stressed. He lost 28 lbs. in 9 months and upon re-examination stated he felt fine. No change in the gastrointestinal x-rays was noted although he was asymptomatic.

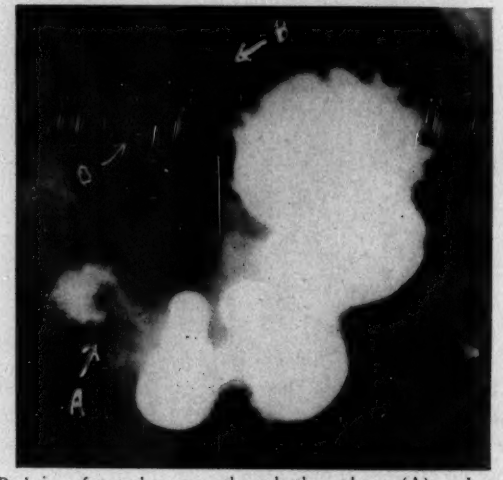

Fig. 2—(Case 2) Prolapse of antral mucosa through the pylorus (A) and gas bubble above the diaphragm due to hiatal hernia (B). The patient's epigastric distress occurred in a recumbent position and was apparently due to the hernia.

Comment:—This patient presented the classical symptoms of hiatus hernia. No specific symptoms could be ascribed to the transpyloric mucosal prolapse.

Case 2 (Fig. 2):—Female, age 64,with chief complaint of cramps in the left lower quadrant, constipation and frequent urination. There was a twenty-year history of occasional mild nocturnal epigastric distress particularly after a heavy meal. Physical examination was negative except for marked tenderness in the left lower quadrant. She was approximately 15 lbs. overweight. X-ray studies revealed sigmoid diverticulitis, hiatus hernia and a marked prolapse of the gastric mucosa through the pylorus. On some of the films the latter suggested a polyp prolapsing into the duodenum. Gastric analysis and stools were normal. Gastroscopy revealed

a normal antral mucosa, but as peristalsis started, the antral mucosa which was smooth was suddenly thrown into folds running obliquely across the posterior wall and floor. These were carried by the crest of the peristaltic wave, becoming parallel to the long axis of the antrum as they reached the pylorus through which they appeared to be extruded. After cessation of peristalsis, the antral mucosa assumed its normal smooth appearance, devoid of folds. No polyp was seen.

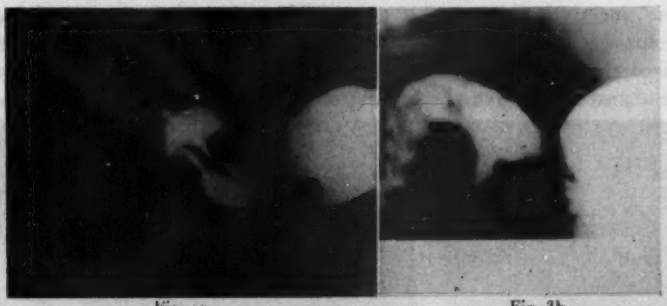

Fig. 3a Fig. 3b

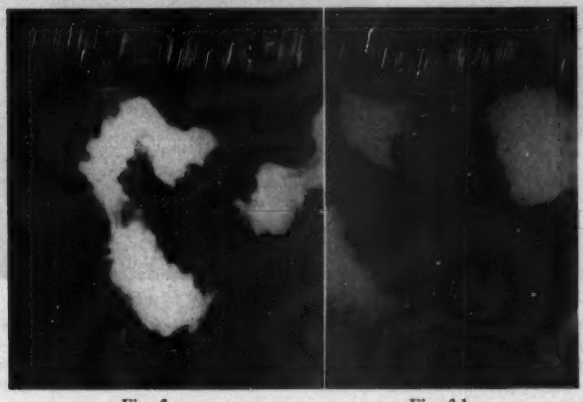

Fig. 3c Fig. 3d

Fig. 3—(Case 3) The variability in the degree of mucosal prolapse is demonstrated in these x-rays which were taken at 24 hour intervals. In Fig. 3a no prolapse is demonstrated; in Fig. 3b one fold protrudes into the duodenum, while two folds are seen in Fig. 3c and a circumferential prolapse is demonstrated in Fig. 3d. A small niche is present on the lesser curvature of the bulb.

This patient was placed on a bland, low residue diet. Her lower abdominal complaints, due to diverticulitis, were adequately managed by treatment of constipation. She was followed for a two year period, and her stomach x-rayed on three subsequent occasions with the same findings and there have been no recurrences of epigastric distress since she has been sleeping in a semi-recumbent position.

Comment:—This patient's chief complaint was referred to symptoms resulting from diverticulitis. Her epigastric distress appeared related to an hiatus hernia. No

specific symptoms could be ascribed to the prolapsing gastric mucosa since relief was obtained primarily by postural change.

b. *Gastritis:*—The view has been advanced[11] that prolapse of the gastric mucosa is the result of hypertrophic antral gastritis, the large and redundant folds being swept through the pylorus during peristalsis. That this same phenomenon can occur in the absence of enlarged folds is indicated by its presence in one case of pernicious anemia[15] with atrophic gastritis. However, the presence of redundant antral folds does favor extrusion of the latter through the pylorus. It must be emphasized that the presence of large folds radiologically is no indication of the presence of antral gastritis and requires gastroscopic and/or pathologic confirmation.

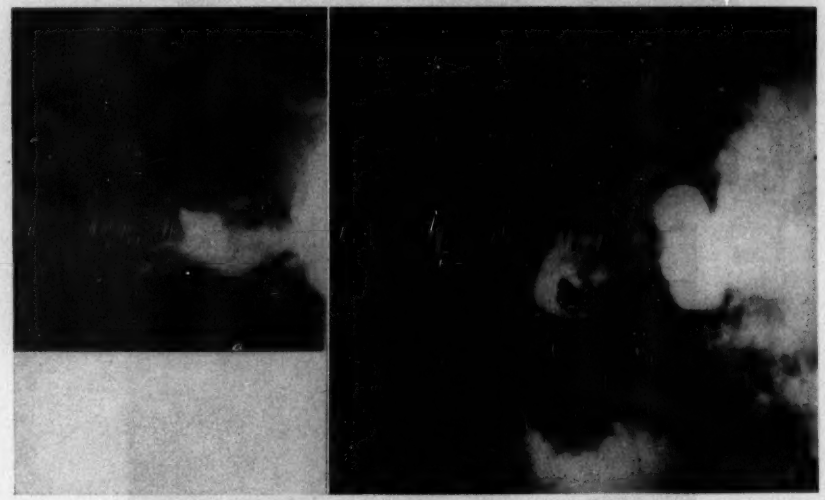

Fig. 4a Fig. 4b

Fig. 4—(Case 4) A large penetrating ulcer projecting from the lesser curvature of the duodenal bulb is seen in Fig. 4a. No significant prolapse of the antral mucosa is seen. In Fig. 4b, taken three months later when the patient was asymptomatic the niche is not seen but marked prolapse of the antral mucosa is demonstrated. The latter did not cause any appreciable clinical symptoms.

Severe hypertrophic gastritis may be accompanied by protrusion of the antral folds through the pylorus in some cases, while in others this phenomenon may be absent. However, it is difficult to evaluate clinically the role played by the prolapsing mucosa in such cases. In one of our patients with a marked generalized hyperplastic gastritis accompanied by a severe degree of transpyloric mucosal prolapse, resection of the redundant mucosa and pyloroplasty failed to relieve his symptoms[16]. This would indicate that where gastritis is more than a localized disease of the antrum, relief of symptoms is not to be anticipated by removal of the prolapsed mucosa. Furthermore, considerable degrees of mucosal prolapse may be demonstrated radiologically in the absence of demonstrable gastritis following surgery or at postmortem.

c. *Peptic Ulcer:*—Melamed[5] found a peptic ulcer in nearly 10 per cent of his cases of prolapsing gastric mucosa. In our experience this estimate is very conservative. Scott[1] differentiates between prolapse of the gastric mucosa and an "anomalous" fold of gastric mucosa which extends across the pylorus into the duodenum. That this distinction is artificial is indicated by the fact that while a single fold may protrude into the duodenum at one examination, two and even more rugal folds may be seen in the same patient subsequently as illustrated below.

Case 3 (*Figs. 3a, b, c, d*):—Male, age 45, a salesman, with a two year history of intermittent "hunger pain" relieved by food had 2 episodes of massive gastrointestinal bleeding. Repeated x-rays were reported as demonstrating a small crater on the lesser curvature of the duodenal bulb. The patient refused surgery and was maintained on a medical regime. The x-rays illustrated in Fig. 5 were taken at intervals of 24 hours, one year after his last hemorrhage and when he was asympto-

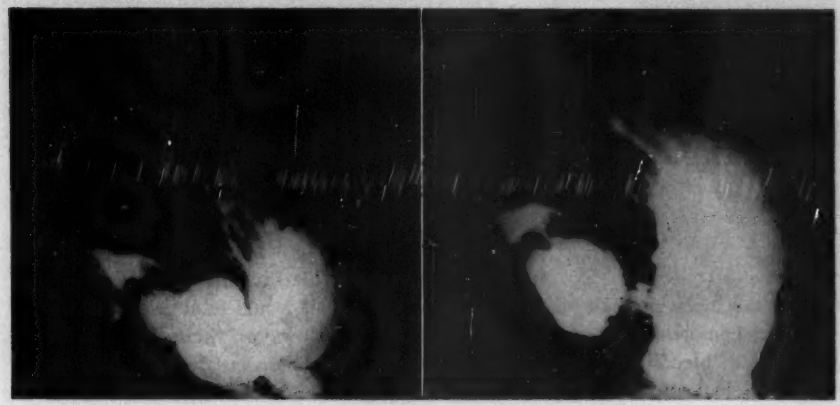

Fig. 5a Fig. 5b

Fig. 5—(Case 5) The mild prolapse of the antral mucosa demonstrated in Fig. 5a was believed to be the cause of massive hemorrhage until gastroscopy disclosed a gastric ulcer on the lesser curvature, seen on subsequent x-ray, Fig. 5b. No prolapsing gastric mucosa was present at the latter examination.

matic. They demonstrate considerable variation in the appearance of the base of the duodenum.

Comment:—An anomalous fold protruding into the duodenum would produce a constant defect which would be present at all examinations. Actually the gastric mucosa is so loosely attached to the submucosa that at postmortem any large fold in the prepyloric region can be readily slid forward to occupy the mouth of the open pylorus.

Many observers report a high incidence of nausea, vomiting and epigastric cramps coming on shortly after eating and precipitated by intussuscepting gastric mucosa as it is caught in the pyloric ring. It would thus be anticipated that duodenal ulcer complicated by prolapsing gastric mucosa would result in a rather bizarre syndrome relatively intractable to the usual medical regime which suffices

in the large majority of ulcers without this complication. The symptomatology and the intractability of ulcer, however, bears little relationship to the presence or absence of transpyloric mucosal prolapse.

Case 4 (Figs. 4a, b):—Male, age 62, with a six year history of epigastric pain between meals and occasionally awakening him at night. His symptoms were always prevalent in the fall. Previous x-rays demonstrated an hiatus hernia and a duodenal ulcer. He maintained no dietary regime except when he experienced symptoms. In November, 1949 he experienced severe persistent pain in the epigastrium which radiated to the back and was not readily relieved by milk or alumina gels. X-ray (Fig 4a) showed a penetrating ulcer on the lesser curvature of the duodenum. He was hospitalized and treated with hourly feeds and his symptoms subsided after 10 days. Re-examination on February 19, 1950 when he was asymptomatic (Fig. 4b) showed deformity of the lesser curvature of the duodenal bulb but the most prominent feature was a large prolapse of the gastric mucosa through the pylorus. Gastroscopy revealed a mild hypertrophic gastritis involving the antrum and body of the stomach. Subsequent x-ray examinations when he was free of symptoms constantly demonstrate duodenal deformity due to ulcer but a considerable variation in the extent of mucosal prolapse.

Comment:—The marked prolapse of the gastric mucosa in this patient did not result in any alteration of his characteristic ulcer symptoms until penetration of the ulcer occurred. In fact the most severe degree of mucosal protrusion was demonstrated when he was free of symptoms.

Several observers[1,6,13] report an incidence of bleeding in cases of prolapsed gastric mucosa which ranged from 21-28 per cent. This would establish it as a major cause of hemorrhage of the gastrointestinal tract. However, there is a paucity of evidence of bleeding in cases of mucosal prolapse unassociated with peptic ulcer. This radiological phenomenon is common in peptic ulcer and is more readily identified than the site of ulceration and hence the latter may be readily overlooked.

Case 5 (Fig. 5):—Female, age 44, with one year history of occasional postprandial epigastric distress experienced sudden onset of melena, requiring hospitalization and 1,500 c.c. transfusions. Physical examination was essentially negative. Bleeding stopped after 2 days and x-rays taken at the hospital 5 days later were reported as negative apart from prolapse of the gastric mucosa through the pylorus (Fig. 5a). The latter was considered to be the site of bleeding. She was referred to the senior author for gastroscopy which was performed one week after the initial x-rays, and a benign gastric ulcer was seen on the lesser curvature. X-ray studies of the stomach (Fig. 5b) two days later demonstrated the ulcer. No transpyloric mucosal prolapse was seen at this examination.

Comment:—In this case a gastric ulcer was overlooked at the initial x-ray examination while the prolapsing mucosa appeared obvious and hence was considered the cause for bleeding. While it cannot be proved that hemorrhage emanated from the ulcer, it seems to be the most logical site of its origin. In many of the case re-

ports in literature citing bleeding due to prolapsed gastric mucosa there is a noteworthy lack of gastroscopic observations excluding other sources of hemorrhage.

Case 6 (Fig. 6):—Male, age 48, with intermittent epigastric pain relieved by food was investigated by x-ray in 1946 with negative results. In November, 1947, while on an ulcer regime, he developed melena for 5 days and was hospitalized. Following x-rays he was told prolapsed gastric mucosa was found. He maintained a bland diet and felt well until December, 1948 when he again noted tarry stools and weakness and was again hospitalized, requiring several transfusions. X-rays were again reported as demonstrating prolapse of the gastric mucosa through the pylorus and an hiatus hernia. Subtotal gastric resection was recommended but he refused surgery. He felt well during the subsequent year on a general diet but because his

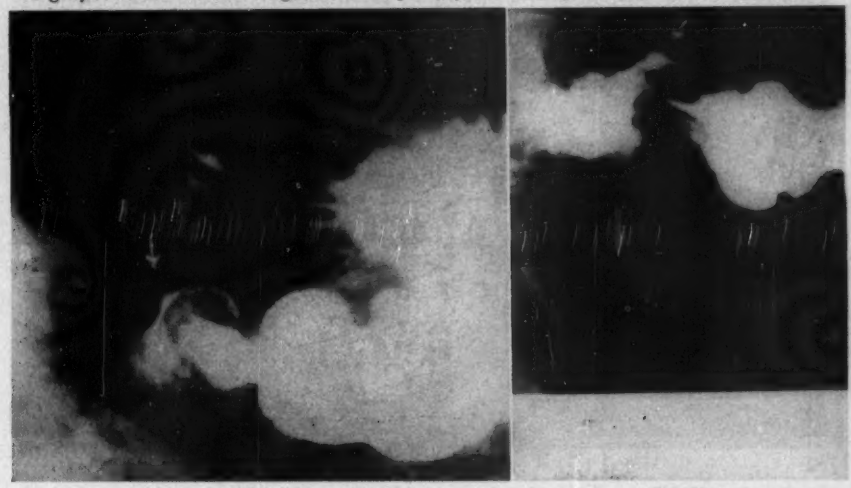

Fig. 6a Fig. 6b

Fig. 6—(Case 6) Patient with repeated episodes of upper gastrointestinal bleeding which was believed to emanate from gastric mucosa prolapsing through the pylorus. Fig. 6a was his third x-ray study and demonstrates a small hiatus hernia and a duodenal ulcer which is almost obscured in a basal view of the bulb. A profile view (Fig. 6b) shows the niche and prolapsing gastric mucosa. At operation, a bleeding duodenal ulcer was found with a ring of antral mucosa protruding through the pylorus. The prolapsing mucosa was reported as normal.

bleeding seemed to occur in the fall each year, he was referred to the senior author on October 6, 1949 for a routine examination. His previous x-rays were not available for appraisal. Physical examination was not remarkable. He was well nourished, being some 15 lbs. overweight. X-rays revealed a small hiatus hernia, a mushroom-shaped deformity of the base of the duodenal bulb due to protrusion of the antral mucosa and a small niche on the lesser curvature of the bulb which was almost completely obscured by the prolapsed gastric rugae (Figs. 6a & 6b). Two weeks later, following a dietary indiscretion, the patient felt nauseous and vomited blood. This was followed by several loose tarry stools and extreme weakness. He was hospitalized and active bleeding continued for 48 hours during which time his pulse

remained rapid and hemoglobin failed to exceed 50 per cent despite 2,500 c.c. blood transfusions. A subtotal gastric resection was done and the resected specimen showed a duodenal ulcer 12 mm. in diameter with a bleeding vessel at its base. A collar of gastric folds protruded through the pylorus and could be slid to and fro with ease. Sections through the prepyloric mucosa failed to show evidence of significant gastritis.

Comment:—In this case the mucosal prolapse obscured a small duodenal ulcer. Apparently the latter could not be demonstrated radiologically at previous examinations.

d. *Carcinoma of the Stomach:*—Prolapse of the gastric mucosa through the pylorus is not a rare incidental finding in carcinoma of the stomach, regardless

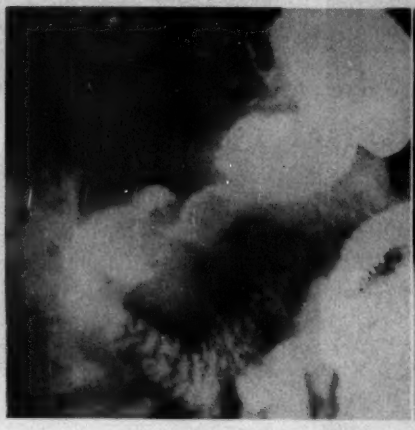

Fig. 7

Fig. 8

Fig. 7—(Case 7) Large carcinoma of the antrum with prolapse of prepyloric mucosa into the duodenum. At operation a ring of antral mucosa protruded 1 cm. into the base of the duodenal bulb.

Fig. 8—(Case 8) Prolapse of the gastric mucosa through the pylorus in a patient with two attacks of biliary colic due to cholelithiasis. There was no previous history of dyspepsia and no symptoms could be ascribed to the mucosal prolapse.

whether the lesion is in the antrum or near the cardia. There appears to be little relationship between its presence and the albumin/globulin ratio or to the degree of malnutrition.

Case 7 (Fig. 7):—Male, age 62, with symptoms of epigastric pain for 18 months. Initially his symptoms were relieved by food and antacids but for the past 6 months he noted anorexia, weight loss and his pain was unrelieved by his usual medication, x-rays showed a large filling defect of the antrum and marked prolapse of the gastric mucosa through the pylorus. A small ulcer was also noted on the lesser curvature below the cardia. At gastroscopy a benign ulcer was seen in the upper third of the body of the stomach and a large polypoid carcinoma filled the antrum and pars media. At operation a subtotal resection was performed and the

three lesions described above were found. The mucosa extruding through the pylorus was not the site of malignant involvement.

Comment:—Rubin[10] reported a case of prolapse of a carcinomatous polyp through the pylorus and this has been repeatedly cited as a possible complication of prolapsing gastric mucosa. Since gastric polyps are liable to malignant degeneration regardless of their site, there seems to be little relationship between his case and the subject under discussion, which pertains to prolapsing mucosa rather than to tumors extruding through the pylorus.

Association With Diseases of the Biliary Tract and Liver

We have observed prolapse of the gastric mucosa in cases of chronic virus hepatitis, hepatic cirrhosis, and in chronic cholecystitis with and without cholelithiasis. In cirrhosis there was no relationship between ascites or the albumin/globulin ratio

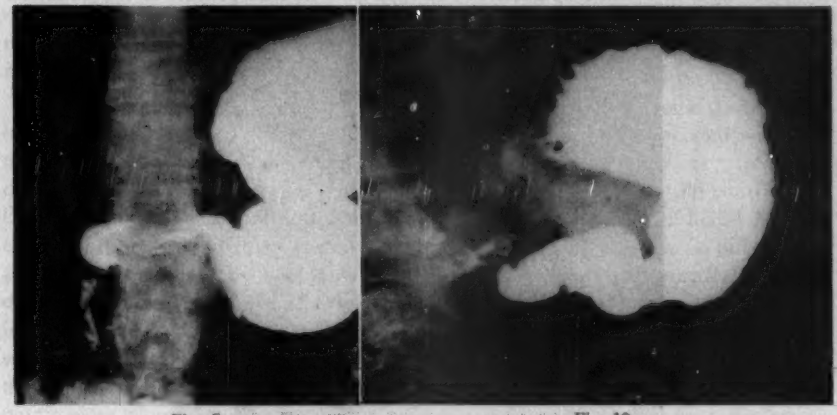

Fig. 9 Fig. 10

Fig 9—(Case 9) Carcinoma of the pancreas as evidenced by pressure defect on the greater curvature of the antrum. There is a smooth concavity of the base of the duodenal bulb which does not present the characteristic lobulated features of prolapsed gastric mucosa, but at operation a large ring of antral mucosa protruded through the pylorus.

Fig. 10—(Case 10) Marked prolapse of the gastric mucosa through the pylorus in a woman with ulcerative colitis. There was no history of symptoms referable to the upper gastrointestinal tract.

and the presence of prolapse. The dyspepsia occurring in chronic hepatitis or chronic cholecystitis may simulate that attributed to prolapsing gastric mucosa. However, the latter was found in patients whose sole complaint was biliary colic and who lacked an antecedent history of dyspepsia, and who were completely relieved of symptoms by cholecystectomy.

Case 8 (Fig. 8):—Male, age 38, was well until January, 1950 when he developed a sudden attack of pain in the right upper quadrant and vomiting. Symptoms subsided in 48 hours and he sought no medical attention.

He was completely asymptomatic until July 2, 1950 when the same type of pain recurred. There was no previous history of qualitative dyspepsia. Physical examina-

tion revealed slight right upper quadrant tenderness. Gastrointestinal x-rays were normal except for prolapse of the gastric mucosa through the pylorus. Cholecystogram demonstrated several small cholesterol stones in the gallbladder. Cholecystectomy was performed July 12, 1950 and he has been asymptomatic since.

Association With Disease of the Pancreas

Transpyloric prolapse of antral mucosa was encountered in carcinoma of the pancreas. The following case illustrates that no special symptoms referable to the mucosal prolapse were present, nor was gastritis found in the mucosa involved.

Case 9 (Fig. 9):—Male, age 47, with four month history of pain in the epigastrium unrelated to meals and radiating to the back, progressive jaundice and anorexia. The essential physical findings were icterus, an enlarged firm liver, and a questionable mass in the mid-epigastrium. X-rays showed enlargement of the duodenal

Fig. 11

Fig. 11—Prolapse of a single gastric fold through the pylorus presenting a polypoid defect in the base of the bulb in a case of duodenal ulcer. This is a common finding in association with duodenal ulcer.

loop with extrinsic pressure on the greater curvature of the pars media, and prolapse of antral mucosa into the base of the pylorus. At operation a carcinoma of the head of the pancreas was found and a Whipple operation performed, but the patient died the following day. The pancreatic lesion had not involved the stomach, and the pylorus was widely patent admitting two fingers. Large antral folds could be readily slid across the pylorus. Pathologic report revealed "Normal gastric mucosa".

Association With Diseases of the Lower Intestinal Tract

Prolapse of the gastric mucosa was found in patients whose symptoms were primarily related to lesions of the intestine or colon. Thus it was seen in intestinal obstruction, Salmonella Newport enterocolitis, amebic granuloma of the cecum, diverticulitis of the sigmoid, carcinoma of the colon and in ulcerative colitis. In the large majority of these cases it was observed during the course of a small intestinal

series since the clinical symptoms rarely warranted detailed studies of the pyloroduodenal region.

Case 10 (*Fig. 10*):—Female, age 52, with a history of frequent grossly bloody stools of 6 months' duration. Eight years previously she had a similar episode which lasted one year and was diagnosed as ulcerative colitis. There were no symptoms referable to the upper gastrointestinal tract. She attributed the recurrence of diarrhea to recent emotional upsets. Sigmoidoscopy and barium enema established the diagnosis of idiopathic ulcerative colitis involving the distal colon and rectum. Prolapse of the gastric mucosa through the pylorus was found during the study of the small intestine.

Discussion

Recent reports indicate that prolapse of the gastric mucosa is not as rare an occurrence as was previously thought. It is our opinion that it is a relatively common finding in various diseases of the gastrointestinal tract many of which are unrelated to the pyloroduodenal region.

To consider it a complication of the disease with which it is associated, would imply that it causes symptoms, *per se*, which are not ordinarily associated with the primary disease. In such diseases as ulcerative colitis, diverticulitis or carcinoma of the colon and cholelithiasis it occurs as a mere incidental finding and contributes little if anything to the clinical symptoms. Since the symptoms of hiatal hernia, chronic hepatitis or chronic gastritis are frequently nonspecific, it is difficult to assess the role played by concomitant prolapse of the prepyloric mucosa. In duodenal ulcer, however, where a fairly specific symptom complex exists, there is little indication that transpyloric prolapse can be considered a "complication" meriting special consideration. It neither renders the ulcer intractable to medical therapy nor increases the liability to hemorrhage. There is no variation in the symptoms of peptic ulcer when associated with mucosal prolapse despite the fact that the latter, when present alone, is purported to cause symptoms quite distinct from the peptic ulcer syndrome.

It has been suggested[6,18] that the intussuscepting mucosa may be the site of bleeding in cases in which peptic ulcer cannot be demonstrated roentgenologically following an episode of upper gastrointestinal hemorrhage. The presence of extruded antral mucosa in such cases should redouble the efforts to find an ulcer since the prolapsing mucosa frequently produces an x-ray deformity of the bulb which may be more spectacular than a small niche. A single fold protruding through the pylorus like a "sentinel pile" is not an uncommon finding in peptic ulcer and its presence should always arouse the suspicion of an associated ulcer (Fig. 11).

A review of reports in literature dealing with bleeding in patients with mucosal prolapse reveals that a duodenal ulcer was present in many, even though it was frequently referred to by the surgeon as "inactive". The question as to whether an ulcer is clinically inactive or whether it has been the cause of a previous hemorrhage cannot be resolved by the surgeon either by visual inspection or by palpation.

Nygaard and Lewitan[18] reported a case of repeated hemorrhage in a patient with extrusion of the prepyloric mucosa into the duodenum. Subtotal gastrectomy was performed and the specimen showed an antral gastritis and a healed prepyloric erosion. The exact source of the hemorrhage could not be ascertained due to the long interval elapsing between the last bleeding episode and the operation. Whether the gastric erosion preceded the onset of mucosal prolapse or whether it resulted from trauma incidental to the mucosa slipping to and fro through the pylorus could not be determined. A discussion of the etiology of transpyloric mucosal prolapse is beyond the scope of this communication and will be reported elsewhere[15]. However, it would appear that the common association of peptic ulcer (usually duodenal) and mucosal prolapse is hardly fortuitous, and that the former is a contributory cause in the pathogenesis of the latter. Furthermore, the usual train of events is first ulceration followed by mucosal prolapse. A similar mechanism occurs in hypertrophy of the pylorus in the adult of which peptic ulceration is a frequent precursor, the hypertrophy becoming progressive even after the ulcer has healed.

The relationship of chronic antral gastritis to mucosal prolapse has not been conclusively established. The majority of resected specimens have been the site of a variable degree of gastritis, while in others no inflammatory changes were found. Severe antral gastritis may be present without the mucosal prolapse and the symptomatology in such cases appears to differ little from those cases in which the rugae slip through the pylorus.

Melamed & Melamed[19] reported this phenomenon in cases of cardiac decompensation which they believed due to edema of the antral mucosa. They further observed diminution in the degree of extrusion after restoration of good cardiac function by appropriate therapy. In this regard it must be emphasized that variability in the degree of prolapse is characteristic of this condition and bears little relationship either to the symptomatology or therapy. Furthermore we have been unable to correlate the degree of prolapse with reversal of the albumin/globulin ratio or the presence of ascites in patients with carcinoma or cirrhosis. It would thus appear that prolapse of the gastric mucosa through the pylorus may be observed in association with many of the common diseases of the gastrointestinal tract. In the overwhelming majority of cases the symptomatology is that of the primary disease with the extrusion of antral mucosa playing an insignificant role in the elaboration of symptoms. Therapy therefore should be directed to the primary disease without special regard to the displaced gastric mucosa.

Conclusions

Prolapse of the gastric mucosa through the pylorus is a common concomitant finding in many pathologic conditions of the gastrointestinal tract. No specific symptoms could be related to the prolapsing prepyloric mucosa when associated with hiatus hernia, peptic ulcer, cholecystic disease or other pathologic conditions of the pyloroduodenal region. Finally, it occurs as an incidental finding in lesions of the lower intestinal tract in the absence of symptoms referable to the stomach.

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MELANOSIS COLI*

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Melanosis coli is a condition in which there is a deposition of melanin or a melanin-like pigment in the mucous membrane of the colon. Apparently the first published reference to this condition appeared in a work by Cruveilhier[1] (1829-1835). Virchow[2] described a case in 1847 and coined its present name in 1858. The condition has been well-known to the pathologist but less so to the clinician. Bockus, Willard, and Bank[3] in 1933 published the first large series of cases in which the diagnosis was established by sigmoidoscopy. This entity has been seen less frequently in more recent years[4] and for this reason we have felt it worthwhile to review the subject briefly and to report a case which has come under our observation.

The color of the pigment varies from gray to brown or deep black depending upon the intensity of the pigmentation and it may be present anywhere in the colon from the ileocecal valve to the anal sphincter. The pigmentation may be diffuse or patchy in its distribution. Many writers[5-8] found the pigmentation most intense in the cecum and ascending colon. In the 41 cases reviewed by Bockus et al[3] it was usually deepest just inside the anal sphincter and less intense as the examination proceeded proximally in the rectum and sigmoid. In a few instances[6,7,9] pigmentation has been found in the terminal ileum and in the lymph glands of the mesocolon.

The sigmoidoscopic picture is a striking one. The areas of pigmentation are irregular, oval, or polyhedral in outline and vary in size from 2 to 10 millimeters. They are usually separated by an irregular network of fine lines of lighter shade although in some locations there may be confluence of these small areas to produce larger patches of discoloration. Observers have variously compared the appearance of the involved mucosa to that of toad skin, snake, crocodile, or tiger skin. These analogies are quite descriptive. However, the mucosa maintains a normal smooth, glistening surface. The pigmentation is usually the only alteration from normal although Bockus et al[3] noted a rather high incidence of slight catarrhal changes in the mucous membrane.

In most instances no other organic colonic pathology is found in melanosis coli but the pigmentation has been found quite frequently in association with carcinoma of the colon. In 43 cases of carcinoma of the colon studied at necropsy Stewart and Hickman[7] found melanosis in 21, an incidence of 48.8 per cent. The pigmentation was usually most intense proximal to the lesion but was also found below it. The melanotic change was believed to be due to concomitant intestinal stasis.

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Microscopically, the surface epithelial cells are free of pigment. The pigment granules are found within large mononuclear cells situated in the tunica propria. Some pigment may be found extracellularly. The pigment deposit usually ceases abruptly at the muscularis mucosae but in rare cases this mucosal layer may be involved[6]. The exact nature of the pigment-containing cells is not definitely known but they are generally believed to be fixed or wandering cells of connective tissue origin.

The etiology of melanosis coli has not been established with certainty and one finds varied opinions in the literature regarding the nature and origin of the pigment. Most of the evidence would suggest that it is melanin or a melanin-like substance. Almost all observers have noted that chronic constipation is a primary symptom in patients exhibiting melanosis. This was true in every one of the 41 cases reported by Bockus et al[3]. Bartle[10] in 1928 was the first to suggest that the habitual use of the anthracene laxatives might be a factor in the production of colonic pigmentation. The importance of this etiological factor has been stressed by subsequent writers. In the series reviewed by Bockus et al[3] all of the patients used laxatives habitually and in each instance, where the type of laxative could be determined, the offending drug was cascara or some other member of that group. Cascara, rhubarb, senna, aloes, and frangula comprise the so-called anthracene group of cathartics and those which have been isolated are derivatives of anthraquinone[11]. The true significance of the anthracene laxatives in the etiology of this condition is subject to question since cases of melanosis coli have been reported who seldom took any cathartics[12]. Moreover, there are patients with chronic constipation who have used the anthracene laxatives and who do not exhibit melanosis[4]. Susceptibility to this type of pigmentation may be an individual characteristic. Corwin[13] was unable to produce melanosis coli experimentally in three dogs by the administration of cascara sagrada and the production of constipation by a specific diet. However, it could be argued that his results might be due to a species difference or insufficiently large sample. Hurst[14] expressed the view that the artificial diarrhea produced by laxatives of any kind taken because of constipation or the fear of constipation results in excessive putrefaction of protein in the colon and that the disintegration products are converted into melanin. However, Bockus[15] states, "I know of no proof that diarrhea *per se,* unless produced by one of the anthracene laxatives, is in any way responsible for the occurrence of melanosis. In my experience, other laxatives producing more liquid movements have never accounted for melanosis coli." The evidence submitted by Bockus et al[3] would tend to incriminate the anthracene laxatives and they feel that these drugs either "contain a pigment or elaborate a pigment within the colon which is phagocytized by the deep mucosal cells producing melanosis coli".

Melanosis coli in itself produces no symptoms and there is no evidence that it is a precancerous lesion. It is usually present in patients with long-standing functional colonic stasis and attention of the clinician should be directed to the correction of this problem. Obviously, the finding of melanosis does not exclude the presence of other pathology in or outside the gastrointestinal tract.

Treatment consists of a bland diet, elimination of all anthracene laxatives, control of constipation with liquid petrolatum or one of the hydrophilic colloid laxatives, and general instructions on the importance of establishing a regular bowel habit time. With such measures relief from constipation will usually be achieved and the colonic pigmentation will usually disappear gradually over a period of months. It may persist, however, and Dodson[16] cites a case in which the pigment was present essentially unchanged for six years.

Case Report

M. S., a 36-year old, white, married, female, was first seen by us on August 26, 1949, with the chief complaints of constipation for some 15 years, intermittent lower abdominal pain for 4½ years, and nervousness. The constipation was obstinate and she had taken cascara every night for 15 years in order to promote bowel evacuation. She had had intermittent lower abdominal pain which she dated back to the time of a spontaneous abortion some 4½ years previously. The pain was sticking or crampy in character, not always in the same place, but mostly in the right lower quadrant, with some associated pain across the lower back. The pain would be severe for 15 minutes to an hour and gradually subside over a period of several hours. The menstrual periods were regular and there was no definite time relationship between the episodes of pain and the menstrual cycle. There was no associated fever, chills, nausea, vomiting, or diarrhea. Prior to her visit to us she had been seen by a gynecologist who had found no significant abnormalities on pelvic examination.

The past history was negative except for a cholecystectomy and appendectomy 15 years previously, a normal spontaneous delivery 6 years previously with death of the infant in the neo-natal period, and a dilatation and curettage 4½ years previously, following a spontaneous abortion.

A general physical examination was negative except for tenderness in the right lower quadrant.

Routine urinalysis was negative. The hemoglobin was 12.8 gm. and the sedimentation rate 24 millimeters in 1 hour (Westergren). Fluoroscopic examination of the chest was negative. Examination of the colon by means of a barium enema was negative except for the finding of a redundant sigmoid. Study of the upper gastrointestinal tract by roentgen examination after a barium meal was negative except for mild pylorospasm.

Sigmoidoscopic examination revealed a striking pigmentation of the mucosa extending from just inside the anal sphincter to as far as the instrument could be passed, a distance of 10 inches. The areas of pigmentation were brown to black in color, irregular in contour, varying in size from 2-10 millimeters, and becoming confluent in some locations. The appearance suggested that of a leopard skin. No masses, ulceration, or bleeding were noted and the mucosa presented a glistening smooth surface. No abnormalities other than the pigmentation were noted.

A diagnosis of melanosis coli and functional constipation was made. Treatment was instituted essentially as outlined above. Initially, oil retention enemata were also recommended every other night.

The patient responded well to this regime and within a brief period she was able to establish a fairly normal bowel habit. Only occasionally was an enema necessary. However, despite marked improvement in her constipation and general well-being, she continued to have intermittent episodes of lower abdominal pain. Approximately two months after her initial examination the sigmoidoscopic picture was unchanged. In February, 1950 she had several severe episodes of pain. When examined during one of these episodes, the temperature and pulse were normal. The abdomen was soft throughout but exhibited slight distention. To the right of, and just below the level of the umbilicus a mobile, slightly tender, tubular mass was felt, believed to be a loop of bowel. Further studies, including a flat plate of the abdomen and serial films of the small bowel, were negative. The colon was negative except for some redundancy and spasm.

Because it was felt that some process other than her colonic disturbance was responsible for her symptoms the patient was referred to a gynecologist who felt that the patient had partial intestinal obstruction in the ileocecal region and advised surgery. On March 8, 1950 the patient was explored and an extensive endometriosis found, which had caused adhesions involving the terminal ileum and cecum. The adhesions were severed and a hysterectomy and bilateral oöphorectomy performed.

To date we have not had the opportunity of a follow-up sigmoidoscopic examination to determine whether there has been any decrease in the degree of pigmentation in the colon.

Summary

Melanosis coli is a condition characterized by a deposition of melanin or a melanin-like pigment in the mucosa of the colon. The etiology is not entirely clear but prolonged colonic stasis and the habitual use of one of the anthracene laxatives appear to be of paramount significance.

Melanosis coli, per se, produces no symptoms but is usually associated with chronic constipation. Other pathology may co-exist.

With proper therapy the pigmentation will usually disappear.

A typical case has been reported.

Addendum

A repeat sigmoidoscopic examination was performed on the above patient August 5, 1950, approximately one year after her initial examination. The pigmentation was still present but was reduced about 30 per cent in intensity and was less diffuse. The pigmentation was more patchy in its distribution and no confluence was noted. It is interesting that the same condition exists to a lesser degree in the patient's mother and sister, both of whom used cascara habitually.

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SYMPATHETIC BLOCK FOR PRESERVATION OF STRANGULATED INTESTINES*

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Under the leadership of Wangensteen new light has been brought into the field of intestinal obstruction. Anatomical and physiopathological conditions have found new interest. The clinical picture has been more clearly described and the important differentiation between strangulated and simple obstruction has been emphasized. Different handling of the various conditions has been worked out. The diagnosis of intestinal strangulation may be easy or very difficult, but more difficult is often the problem which faces the surgeon when he visualizes the affected intestines. The most important question is whether the intestines are still viable or not, and in consequence whether to resect or not to resect. Wangensteen states that it is difficult, sometimes impossible, to be certain by any method of examination to eliminate borderline cases. Owings and Smith made the remark that the more experienced the surgeon the harder it is to decide. Lack of courage to be radical, when necessary, may cause the patient's death, and too much activity in a case which may have survived without resection may have fatal consequences too. We know that bowel resection in the presence of strangulation is a very dangerous procedure and increases the operative hazard enormously. Only a few years ago the mortality percentage in the best clinics was still between 40 and 50, while for simple lysis of adhesions and nonresective repair the mortality showed only 14.8 per cent. Better knowledge of pre- and postoperative preparation, better management of the chemical and electrolytic necessity, extensive use of antibiotics, and improvement of the technic, have changed the statistical results, but the mortality is still frightfully high.

Therefore, every new method of diagnosis and of therapy concerning viability of strangulated intestines is of importance and justified.

Laufmann and Method have worked on the question of strangulation and have stated that we have 3 different pathological entities composing the strangulation. They are: the closed loop, the mesenterial vascular occlusion, and the simple proximal intestinal obstruction. The mechanical condition of the closed loop caused by a band, by a hernial sac, or by a volvulus can be easily understood. The fact that the proximal loop to an obstruction becomes dilated makes no difficulty in conception either. It is more difficult and more complicated to understand the changes of the vascular root of the affected loop. The occlusion of the vessels may be of 3 different types: the arterial, the venous, and the combined occlusion. The components may be mechanical and neurodynamic. As a typical example of arterial occlusion we can select the mesenterial, arterial infarction. The arterial occlusion is a primary

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condition. It is followed by proximal and distal spasm, first of the arterial trunk, and second by affection of the vein. The affected loop appears pale, blanched and rippled, no petechiae or bleeding are seen, either in the intestinal wall or in the mesentery, or in the surrounding vessels. From other parts of the body we know that in addition to the occlusion the spasm is of utmost importance, and of dangerous sequel to the obstructing mechanism (Mulviall and Harvey). The damage caused by vascular occlusion is the addition of both factors. In consequence if no relief sets in, collateral circulation may be blocked because of spasm along the entire vascular bed and gangrene follows. If arterial strangulation is released we see a paradox response. Through the remaining partial spasm the blood is retained, hyperemia caused bright red color, and the muscular spasm finds its expression in larger peristaltic waves. It is important that this arterial spasm does not persist because in case of a longer period of this mechanism the beneficiary response will be less outspoken and tissue damage may occur. It is still uncertain whether this response of the tissue is caused more by the chemical products of tissue anoxia or sympathetic reflex. In most of the cases of intestinal strangulation we face the phenomena of venous occlusion. The compression of the venous trunk causes first visible response in engorgement, and bluish red to purplish discoloration. The thrombus develops. Increased arterial blood supply tries to overcome the block but the hypertension is soon followed by a more feeble action which finally causes a stopping of the arterial blood flow. The capillaries become completely filled to capacity, extravasation of blood cells and plasma into the tissue sets in: a very peculiar reactionary condition of spasm and relaxation in the arteries and arterioles follows and in consequence there is more swelling, more stasis with extravasation. Bloody transudations enter the peritoneal cavity. Edema increases, more compression occurs, and in a vicious circle gangrene sets in. As soon as the condition has advanced it is very difficult to decide which factor causes the momentary actual change, whether it's mechanical, dynamic, or toxic chemical. As soon as gangrene has developed viability has logically disappeared, and further preservation is impossible. But there are conditions where gangrene is very close by and where we may still save the bowel.

Proof of viability can be seen in the following factors: Pulsation of the vessels, good color of the intestine with glistening of the serosa, noticeable peristalsis, and a positive fluorescent test. The three first described factors are well known, and it is not necessary to give any further explanation of their importance. The last test was introduced for vascular occlusions by Wolheim and Lange in 1934: In 1942 Lange and Boyd published further studies of this test and in later publication Lange and his associates presented cases of successful use in strangulations. Five to ten c.c. of a 5 per cent solution in 5 per cent sodium bicarbonate is injected into the cubital vein. After some minutes with the ultraviolet light and a special wood filter the appearance of fluorescein can be noticed in the tissue if the circulation is still so far patent that viability may be restored. He describes 3 cases with successful use of this method. The literature does not show too much response except for the fact mentioned in papers by Wangensteen, Lufer and Hatfield. The difficulty is that

those operations are often performed as emergencies, often during the night with limited personnel and with medication and special ultraviolet lamp being unavailable. The objection made that it is too complicated and that surgeons do not like to be in a dark room waiting for the response to the test is not justified in my opinion. Another method to test the viability and at the same time to improve the circulation in the damaged bowel is the use of the sympathetic block. In many experiments and in clinical investigations it was shown that the dangerous consequence of vascular occlusion and subsequent spasm can be minimized and even entirely eliminated by the interruption of the vasoconstricting impulse. It was presented originally on the occlusion of the peripheral vascular system, and as early as 1931 Reichert could show marked improvement with the alcohol block of the sympathetic ganglion. Many surgeons who remember the days when we tried to do abdominal surgery under splanchnic anesthesia know how enormous the hyperemia in the abdominal vessels developed. Bleeding was terrific, almost out of control. Patients often went into shock because they bled into their splanchnic field. If we can influence the blood supply of the mesenteric vessels we should be able to use it for the preservation of strangulated bowel. The sympathetic ganglia of the abdomen start on the ventral lateral surface of the second lumbar vertebrae: the celiac plexus lies on the ventral surface of the aorta and the crura of the diaphragm. It surrounds the celiac and the superior mesenteric arteries. It includes the large ganglion on either side, the semilunar ganglion and a series of smaller ones. Besides the sympathetic nerve supply from the ganglia and along the vessels we find sympathetic plexiform structures between the lung and circular muscles of the intestinal wall. Very few articles can be found in the literature about the advisability to influence the sympathetic system for diagnosis of the viability and for the improvement of strangulated intestines. As stated above Herrlin, Glasser and Lange, give the report of 3 cases, mainly stating the diagnostic value. Laufmann and Method found some value in it, especially combined with papaverin. In 1947, Forget reported in a Paris surgical society that he had used novocain injections around the edge of the bowel for about 3 years. He was surprised to see the excellent results and advised its use. Mario Pope in Italy tested the efficacy of this method by animal experimentation. One per cent injections showed best results when injected into the wall immediately adjacent to the strangulated bowel.

I was faced with the problem to try the utmost in a very difficult case where radical surgery definitely would have killed the patient. At that time I did not know about the existing literature and the experiments done previously. Since I was successful in that case I tried it in 4 following cases with fortunately good results.

Case 1:—A 30-year old female was admitted to the hospital with a 3 day history of diarrhea and vomiting. Under observation in the hospital her condition grew worse, and when seen by me had the typical picture of a generalized peritonitis. It was not possible to decide whether the appendix, gallbladder or any other part of the intestines was the cause of the peritonitis. At operation, a strangulated hernia of Treitz was found with a large amount of hemorrhagic fluid which later proved

to contain bacterium coli. The strangulated bowel was carefully dislocated from the paraduodenal cavity, no pulsation was visible. The color was dark purplish. No glistening of the serosa and no peristalsis were seen. About 3 feet of bowel were affected. I injected 20 c.c. of novocain to the area of the second lumbar vertebra as advised by Braun. The left liver lobe was carefully lifted with a retractor, with the left index finger the aorta was pushed to the left side, and the finger kept resting on the anterior surface of the vertebra. With a long spinal needle, about 12 cm. in length, the injection was carefully done. Some novocain was injected more laterally. After this injection novocain was injected along the mesenteric roots and along the edge of the intestine. Warm pads were used to cover the intestine. The change which occurred was so astonishing that I decided to wait. After a few minutes pulsation was noted. Some peristaltic waves could be seen. I decided therefore to finish the operation by infolding the hernial sac and by closing the abdominal cavity with through and through stitches. The patient was nourished with intravenous infusions. A Levin tube was inserted into the stomach. The postoperative course was smooth, and the patient was discharged well.

Case 2:—A six-week old child had incarcerated hernia on the left side, which was reduced in hanging position. Two days later the child became ill with signs of intestinal obstruction. The diagnosis was verified by x-ray. On the left side no hernia was found, but on the right side a hydrocele was present, probably with strangulated hernia above. At operation a strangulated loop of ileum was found, dark purplish, with swelling of the mesentery, with damaged vessels and no peristalsis. When the decision was made to resect the anesthetist reported cardiac and respiratory arrest. With artificial respiration, with increased oxygen inhalation and coramine injection, the child started to breathe again. The heart action was still very weak. The shortest life-saving procedure was indicated. One per cent novocain was injected around the vessels and along the edge of the mesentery. The abdominal wall was closed with through and through sutures, after noting marked improvement in appearance of the bowel. A Levin tube and a Miller-Abbott tube, oxygen tent and intravenous feeding were used and the child recovered completely.

Case 3:—A 52-year old female patient was admitted with symptoms of intestinal obstruction. Patient had a gynecological operation 3 years before. On examination showed a high small intestinal obstruction, the x-ray picture presented collection of air in the 3rd portion of the duodenum. After intake of small amounts of fluids patient started to vomit immediately. The diagnosis of an internal hernia, possibly of the ligament of Treitz was made. A band strangulation caused by adhesion from the previous operation could not be excluded.

Following incision collapsed bowel was found in the lower part of the abdomen. In the upper abdomen a typical hernia of Treitz with strangulation was seen. Only one loop left the hernial sac, because the proximal end was the highest jejunal loop under the ligament of Treitz. Bad smelling hemorrhagic fluid was present (the bacteriological examination proved the presence of B. coli). Gangrene had developed. The intestinal wall was paper thin, black green, no question of viability. The

mesentery showed mesenterial infarction. A resection had to be performed. After releasing the obstructed strangulated bowel the same was packed into pads in order to prevent leakage. Only a very short stump of jejunum was viable. A quick resection of the jejunum 112 cm. long with the mesentery 17 cm. in width was performed. Because of the short proximal end and the bad circulatory condition a block of the celiac ganglion area as described before was done with 20 c.c. of procain sulfate. The change of the color of the intestinal wall was almost miraculous. It changed from a purplish pink almost to a strawberry red. Pulsation could be noticed. The short loop, not longer than about 5 cm. was anastomosed end-to-side to the distal jejunal end. Novocain was also injected along the mesenterial vessels. The hernial sac was implicated in order to close the large paraduodenal opening. The abdominal wall was closed with through and through silk sutures.

The postoperative course was very stormy. A prerenal azotemia developed, the patient had a urea nitrogen of 85. Under careful intravenous feeding and in cooperation with the medical staff the patient improved very much. She was discharged without complaints in a very good condition.

Case 4:—The patient, 65-years old, was admitted with complete signs of intestinal obstruction. Although a hernia was noticed on admission no direct connection between the hernia and the intestinal obstruction could be established. Since the man was a known cardiac in condition of decompensation the medical consultant objected strictly to any surgery unless it was of utmost life-saving necessity. But their prognosis was practically at fault. Miller-Abbott tube was given and the patient improved very much. After a few days the temperature went up. The patient started to vomit again. Even with the Miller-Abbott tube low in the small intestinal tract he became more and more distended and the x-ray showed fluid levels. The hernia was larger than before but could be reduced with slight difficulties. The possibility of a partial reduction en bloc was discussed. The rise in the temperature, the increased signs of obstruction, the x-ray findings made the surgical intervention necessary even against the objection of the medical consultants. On operation a Richter hernia was found with complete necrosis and fibrinous seropurulent peritonitis in the left lower abdomen. A large loop of ileum showed severely damaged serosa, lack of pulsation and peristalsis infiltration and extravasation into the mesentery. On the attempt to free the adhesions in order to resect, necrotic tissue was found in between the adherent loops. Because of the danger of spillage no further attempt at resection was made. Two heavy silk strings were brought from one loop to the other in the form of a mattress suture and tightly closed as necrotising sutures. A Lembert suture layer was carefully performed above. Novocain was injected into the mesentery and along the intestinal border and the abdominal wall closed with through and through sutures. Patient received intravenous feeding, antibiotics. The Miller-Abbott tube was left in the intestinal tract until the first gas was expelled. The patient was discharged in very good condition. He returned 6 weeks later with a new attack of intestinal obstruction. On operation a simple band adhesion was found. The anastomosis was well functioning. The band

was severed. The abdominal wall closed. The postoperative course was smooth. The patient was discharged well. No circulatory or cardiac trouble developed during the postoperative period.

Case 5:—A 29-year old female was admitted to the gynecological service with severe abdominal cramps. She was nauseated and had been vomiting for 3 days. She was operated on 3 years ago for a gynecological condition and the appendix was removed at the same time. The abdomen was very painful on day of admission; 15,000 W.B.C. were found. While patient was observed on the ward she went into an acute severe shock with no blood pressure obtainable. The surgical staff was consulted, the diagnosis of an intestinal obstruction with probable volvulus made, and surgery advised at the earliest possible time, as soon as patient was out of shock. Intravenous infusions were given; oxygen inhaled. Under almost superficial anesthesia a long right rectus incision was made. Hemorrhagic fluid was found in the peritoneal cavity. At one point the lower ileum was adherent to the peritoneal scar and the loops above showed a complete volvulus of at least two feet. The color was dark blue, no peristalsis, no glistening of the serosa, the mesentery was infiltrated with many hemorrhagic extravasations. No pulsation of the vessels in the area. The adhesions were severed; the volvulus rerotated. The patient was almost in complete shock again. No radical surgery could be performed. No blood pressure could be taken. Therefore, 20 c.c. of novocain were injected along the vessels and along the border of the intestines. The change watched for a few minutes was startling. Peristalsis set in; the color improved; pulsation could be noticed. Hot saline solution was poured into the cavity and the abdominal wall closed with through and through sutures.

The patient was brought into an oxygent tent, she was fed intravenously for a few days with a Miller-Abbott tube inserted. The condition improved slowly. About ten days later a fecal fistula developed. It may have been caused by a through and through suture which caused an inside loop after disappearance of the distention. The general condition improved more and more. The fistula was closed at a later date and the patient is now in excellent condition.

It may be stated that in all those cases the well accepted routine of putting hot pads on the affected bowel was observed. That the mechanical release was at least of as much importance as the injection of the novocain, is without doubt. The block of the sympathetic nerves should be considered as an important adjunct of therapy.

Summary

Strangulation of the intestine is characterized by closed loop, strangulation of vessels and simple proximal obstruction. Closed loop and proximal obstruction have to be relieved by mechanical means. The vascular damage is a combined mechanical and dynamic process of occlusion and vascular reflex spasm. Viability of the intestine cannot be judged exactly by color, pulsation and peristalsis alone. The fluorescein test is of importance. The blocking of the sympathetic nerve, either by injection of novocain into the celiac ganglion or by injection into the edge of the

intestine and along the vessels eliminates the spasm. Response to the injection will show change in color, pulsation and peristalsis. If improvement is seen, conservative measures are justified. If result is missing the amount of resection may be reduced by improvement of the vascular condition in the surrounding area. One per cent novocain or procain are to be used. Five cases of successful use of this method are described.

NUTRITIONAL DISEASES OF THE MOUTH AND THEIR DIFFERENTIAL DIAGNOSIS*

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The diagnosis of nutritional diseases is still mainly an art and not a science. The variations of the patients, of the observers, and the lack of precise biological quantitative estimations in all instances, create confusion in the field.

A nutritional deficiency disease is caused by nutritional inadequacy. The latter results whenever adequate amounts of essential nutrients are not supplied to tissues requiring them for normal functioning. Nutritional inadequacy may be caused by dietary inadequacy. This is the primary deficiency. It may also result from environmental conditions or bodily states which interfere with ingestion, absorption or utilization of essential nutrients, or from factors that increase the requirement or cause the destruction or abnormal excretion of these nutrients. This type is secondary or conditioned.

Time is an important factor in the development of nutritional deficiency lesions, for the rate of development of a tissue change will influence its gross alteration. The time may be short or long depending on the amount of nutrient reserve and the severity of the dietary inadequacy. When nutrient reserves are sufficiently exhausted tissue depletion occurs. Tissue depletion is followed by biochemical "lesions", functional changes, and finally anatomic lesions. No step in the chain is necessarily complete before the next begins.

Lesions are described as acute, subacute, and chronic. These terms designate the speed of change in the pathologic picture. Acute lesions are rapid in development, progress, and recession, if properly treated. Chronic lesions are slow in development, progress and in recession. Some may be irreversible. Subacute lesions are intermediate. The velocity of the lesion is determined by the rate of change in tissue concentration of the essential nutrient. Sudden change to grossly inadequate intake with limited reserves will result in rapid change. Chronic lesions represent pathologic changes initiated by slow changes in tissue concentration of an essential nutrient. The pathologic lesions of nutritional inadequacy have in addition the factor of intensity and duration, all of which influence the presenting clinical picture and the response to therapy.

The complete diagnosis of nutritional diseases which includes an evaluation of etiology, depends upon evaluation of the clinical signs, dietary and medical history, routine and special laboratory findings. Most malnutrition is not of the advanced florid type classically seen in starvation, protein deficiency, pellagra, scurvy, beri beri and the like. It is less severe and less fully developed. With few exceptions, the signs are nonspecific and according to most authorities may be produced by factors other than malnutrition. No single sign is necessarily diagnostic or

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pathognomonic; each must be evaluated in the light of the history and of other signs and symptoms. Bilateral polyneuropathy is seen in beri beri—but may occur in diabetes, infections, or after exposure to various intoxicants. Cheilosis is seen in riboflavin deficiency but it may also be due to exposure, iron deficiency, fungus infestations or allergic sensitivities. Corneal vascularity may be due to other causes than riboflavin deficiency. Finally, deficiency disease is frequently multiple, so that the resulting clinical picture is often complex.

Our consideration of nutritional deficiencies will concern itself with lesions of (1) the gums, (2) the tongue and mucous membranes of the mouth and (3) the lips.

Lesions of the gums are those of acute scurvy and the so-called chronic gingivitis. In the adult scurvy is characterized by a long latent period (3-12 months) of a severe inadequacy of ascorbic acid in the food. Swelling of the gingivae and their loosening from the teeth occur early. Intercurrent infection is likely to precipitate the classical picture. Treatment with adequate amounts of Vitamin C results in obvious clinical improvement in 2 or 3 days with clearing in 7 to 14 days. Gingivitis is much more frequently seen in many population groups. Normal gingival tissue is characterized by its light pink color. The interdental papillae filling the spaces neatly, and the remainder of the marginal gum tissue is firmly in contact with the teeth, but is not attached to them. The free margin may be up to 2 mm. in depth. The first sign of inflammation is seen in the marginal gum tissue and the interdental papillae. It is characterized by redness, swelling, tenderness and bleeding on pressure, the gums are shiny. As the condition progresses the labial and buccal areas are involved, and the deeper gum tissue is detached. In the progression of the chronic changes the gums become thickened, pale, and develop a hard leathery consistency giving the impression of increased fibrous tissue. Many factors local and general, nutritional and non-nutritional, are involved. Suggestive evidence that a low intake of ascorbic acid influences the development of gingivitis is the fact that in certain countries such as Newfoundland, where the ascorbic acid intake is low, gingivitis is almost universal, whereas in other areas as in the British West Indies, where the Vitamin C intake is high, gingivitis is almost never seen. After local treatment, a low ascorbic acid intake over several months is associated with a high incidence of recurrence of the gingivitis, while an adequate intake is associated with a low recurrence rate. The gingivitis of this type in contrast to scurvy, when primarily due to malnutrition, is associated with only partial depletion of nutrients over a longer period of time.

Nutritional lesions of the tongue are manifested by both color and anatomical changes, and are primarily the result of B-complex deficiencies. The three characteristic color changes are:

(1) Scarlet red, seen in pellagra and in sprue. The papillae on the tip and lateral margins are first affected, usually associated with redness of the buccal mucous membranes especially around Stenson's duct. As the lesion progresses the entire tongue and buccal mucous membranes are involved. There is also soreness,

edema of the tongue and increased salivation. Ulcerations soon develop in which one finds Vincent's organisms. The lesion is usually superimposed on various grades of glossitis. Adequate treatment with niacinamide in pellagra results in a dramatic improvement in 24 hours and complete cure in 5 to 7 days. A similar response occurs in sprue after treatment with B_{12} or folic acid. Occasionally such tongues may fail to respond to the vitamins and crude liver extract given parenterally but will respond to protein administration. It may be that some amino acid was necessary to complete the enzyme system for niacin or folic acid, or that the deficiency of the protein per se was responsible for the glossitis.

(2) Beefy red glossitis resembling raw beefsteak probably represents a subacute deficiency of niacin or less frequently of other members of the B-complex. It is one of the most common types of glossitis encountered.

(3) Magenta tongue is a purplish discoloration, frequently associated with angular stomatitis and dermatitis and is usually the result of riboflavin deficiency.

The other tongue lesions are those we describe in the stages of chronic glossitis. The earliest lesion consists of hypertrophied fungiform papillae in the anterior third. The end stage is characterized by complete atrophy of both fungiform and filiform papillae. Between these two stages the papillae go through the following sequence: hypertrophy, flattening of the tips, fusion, and atrophy. The fungiform and then the filiform papillae are involved. Innumerable stages are therefore seen between the two extremes first mentioned. The progression of these lesions may be slow or rapid and may stop and remain stationary at any point. Chronic glossitis has been attributed to deficiencies of one or more of the B-complex vitamins, particularly niacin, B_{12}, riboflavin, and folic acid. However some furrowed or geographic tongues are congenital or even due to fungus infections, and lues.

The most common lip lesions are those of riboflavin deficiency. They are manifested by changes in the exposed mucosa, cheilosis, and by changes at the angles of the mouth known as angular stomatitis. At the onset, cheilosis is characterized by edema and soreness. The lips are pale or may show increased redness and denudation along the lines of closure. There may be general desquamation, ulceration and crusting. There is an increase in the vertical markings and this may extend out into the surrounding skin. As the lesion progresses the lips become thin and atrophic in the chronic state. Malnutrition, however, is not the only factor responsible for cheilosis, it may be due to continued licking, sun, wind, cold, chemical irritants and allergic reactions.

Angular stomatitis manifests itself as a pallor, erythema, or slight maceration of the mucosa in the angles of the mouth but later may spread up and down to involve an area of skin adajacent to the angles. As the lesion becomes chronic, wartlike excrescences develop with or without fissuring. The fissures are usually bilateral but may involve one side more than the other.

These lesions—angular stomatitis and dermatitis and fissuring are not necessarily specific for riboflavin deficiency. They may be caused by iron or protein

deficiency, also by ill-fitting dentures, edentulousness, chronic drooling and deep mental folds.

I would like to emphasize therefore that the signs of nutritional deficiency are nonspecific. Malnutrition may be provoked by conditioning factors in persons with an adequate diet, acute and chronic lesions differ from each other in onset, development and in response to therapy, and finally deficiency disease is usually multiple.

To make the correct diagnosis, in addition to the complete medical history and physical examination, one should also check the dietary history and carefully search for possible conditioning factors. As for treatment, to insure the patient's return to normal—one must supply not only the specific nutrient obviously deficient —but the other known nutrients as well—one must supply an adequate qualitative and quantitative level of protein and insure nitrogen balance.

Discussion

Dr. I. Snapper:—The collection of photographs we have seen this morning is really a very interesting one.

It has been said that cheilosis may be due to iron deficiency, and atrophy of the tongue to pernicious anemia. Now it is true that cheilosis often occurs in the anemia of iron deficiency, but this does not prove that the cheilosis is due to the iron deficiency. In this anemia there is impairment of intestinal absorption. The nonabsorption of iron causes the anemia, the insufficient absorption of the Vitamin B-complex, the cheilosis. If in such patients iron alone is administered, then the anemia disappears but the cheilosis persists. If on the other hand large doses of Vitamin B-complex are given parenterally, but no iron is administered, then the cheilosis disappears but the anemia persists.

The same holds true for the atrophic tongue in pernicious anemia. In certain countries this disease is never accompanied by an atrophic tongue or glossitis, and in such areas the physicians don't accept the idea that connections could exist between pernicious anemia and glossitis. In countries where good diets and vitamins are popular, glossitis in pernicious anemia is rare, in countries where the vitamin intake is relatively small, pernicious anemia is usually accompanied by an atrophic tongue. This atrophy of the tongue which is often considered to be due to the anemia, is actually caused by the impaired intestinal absorption of certain substances,—one of the constant signs of pernicious anemia. Therefore in anemia due to iron deficiency there is frequently cheilosis, in pernicious anemia atrophy and inflammation of the tongue, but these two signs actually depend upon an insufficient absorption of vitamins and not upon the anemia.

In avitaminosis C the changes of the gums present one of the most important diagnostic signs. However, this is only true when teeth are present, because in scurvy patients in whom the mouth is edentulous, as in infancy and senility, no gingival changes occur.

It is quite true, as Dr. Fein has insisted, that in scurvy the changes of the gums are not only due to avitaminosis C but that coincidental poor nutrition, especially poor protein nutrition also plays a role.

It is interesting that in the same population where, due to hypovitaminosis C the condition of the gingivae is poor, the teeth are very good, and caries is rare. Evidently there is complete dissociation between the condition of the gums and caries.

The jaw is a remarkable bone, which contains red bone marrow even in the adult. Since red bone marrow reacts very rapidly, the jaw bone may already present lesions in generalized diseases of the bones, even when the rest of the skeleton is still apparently normal. In hyperparathyroidism the jaw is often involved, and there are even cases where the only bone lesions are found in the jaw. In every patient with multiple giant cell tumors of the jaw, or with multiple so-called osteofibromas of the jaw, where, often a few giant cells are also found, hyperparathyroidism should be considered. Each case of giant cell tumor or epulis of the jaw needs a careful study of phosphorus and calcium metabolism with x-rays of the whole skeletal system, because these benign tumors are often pilot signs which indicate a generalized disease although the lesion seems to be completely localized in the jaw.

Dr. O. H. Wangensteen:—It is a pleasure to be with you again. I see among the audience some familiar faces. I was just thinking I had not been in this grand hotel since it changed its name and had its face-lifting operation which brought color into its life. And we too have seen some changes in our methods and now, as we have just seen, these beautiful slides have brought renewed color and interest into our lives.

As you know, John Hunter had some very novel ideas; amongst others, he believed that gonorrhea and syphilis were the same disease. He was so ardent in his belief about this, and being an experimentalist and there being no suitable experimental animal, he rubbed the "common virus" of the two diseases upon his glans penis. And as you remember, he not only contracted gonorrhea but developed a chancre as well! A circumstance which delayed his marriage to Anne Hone for four years.

Some of you remember that when Hunter died, as I recall it, there were no tangible evidences of syphilis in his aorta but he did have coronary sclerosis and a gallstone; those who affect to cure angina pectoris with excision of the gallbladder, should remember this little historical item about Hunter, and the presence of the two diseases.

We hear a lot about the "mirror of the mind". I can well understand from this nice review of pictures, why the old-time doctor said, "Stick out your tongue". Apparently there are a lot of things to be seen on the tongue which serve to inform the child why a person in question is old. Any child can tell the difference between an old man and a young man, without asking his age or looking at his hair to see if he has any, or what its color is. The texture of the skin, his stance and his gait tell a great deal. It is strange, I suppose, that we don't pursue some of these in-

quiries further to see whether there might not be smears, imprints, or stains, made of the mouth from which, on magnification with the microscope rather than by the naked eye, we could tell more.

No one can tell, so far as I know, whether a person has an old stomach or a young one, or an old intestinal canal, or a rectum which is old or young, but these differences are very obvious in the skin. No one said anything about age changes in the tongue. I think these learned gentlemen who have made this field their special study, or Professor Snapper, might tell us from the knowledge and wisdom of their experience, something about that.

I might say something about cancer of the mouth. We know very little about clinical carcinogens. There is ultraviolet light. A person who works in the wind and sun, and therefore has his lips exposed to ultraviolet light, is likely to have cancer of the lower lip. We know there are sex differences as they show up in the vital statistics. Is the sex factor a related item here?

We hear a lot about smoking and syphilis as being a part of the picture in certain cancers. Syphilis it is said, may play a part in cancer of the mouth, esophagus, and even the cervix. Smoking may play a part in mouth lesions. Ultraviolet light has been demonstrated to be a carcinogen. Are there co-carcinogens, that lessen the time for the development of certain cancers in Man?

Not all of us will attain the Biblical three score years and ten concerning which, you may remember too, the Psalmist said: "If by strength thy years be four score, yet is that strength but labor and sorrow." That may be something apart from the situation here, but it is something for us to think about in our struggle to make lives longer. We need to devote much time to the consideration of making them happier.

I just say this with reference to the incidence of cancer. Cancer of the mouth is largely restricted to males. Take the hypopharynx, however. Ahlbon, who has succeeded Berven, as head of the Radiumhemmet in Stockholm described in the *British Medical Journal* (1936) the circumstance that 40 per cent of observed cancers of the esophagus in women were to be found in the hypopharynx. Achlorhydria, anemia, evidence of iron deficiency, and sometimes the Plummer-Vinson syndrome were described by Ahlbon as usual findings in such cancers. Take the incidence of cancer of the lip; that is a predominantly male cancer. Why is cancer of the hypopharynx predominantly female?

No one said anything about stone in the submaxillary duct. That certainly is a common occurrence. Parotitis and mumps, affect the parotid gland. When one has calculi, it is the duct of the submaxillary gland that is involved. Why these particular organ sites? More attention to the nature of tissue predisposition to certain diseases would certainly be in order.

One of the authors, speaking of the tongue, mentioned hairy tongue, a condition which bothers patients sometimes, and clinicians too for that matter. Nothing was said about the therapy of this condition, and I hope that Professor Snapper, or

someone else will speak about the therapy, if any, because therapy, I am certain, is an item in which you are all interested.

Leukoplakia is a condition which bothers the surgeon. One knows you can produce it by a diet low in Vitamin A and, so willy-nilly, most of us who see leukoplakia in the outpatient clinic put these patients on high Vitamin A intake and high Vitamin C for extra measure. And as clinicians, we probably need to distinguish more frequently than we do, in certain conditions, whether to employ fat soluble or water soluble Vitamin A.

It is very obvious, with the discussion we have had, that the tongue can be a useful item in diagnosis. And I want to add, too, that it affords me real pleasure to have as co-coordinator on this program, the distinguished internist, Dr. Snapper. Some of you will remember that when Conrad Bernhard von Langenbeck—who started so many surgeons on their academic careers in Germany—when he began publication of Langenbeck's Archiv, back in the 1820's, wrote a little foreword in which he distinguished the scope of medicine and surgery. I don't know whether Professor Snapper, as a distinguished internist, feels there are any high fences now between these areas or not, but Langenbeck called the surgeon the "externalist", and the internist, the physician, the "internalist". These areas of work for each stuck until anesthesia came into being, followed by the development of aseptic surgery. Then the abdomen became the great gridiron of the former externalist, who disavowed any limitation of his activity there. He didn't want to be fenced in, so to speak. He moved around freely in this new playground, sometimes giving very little evidence in which direction he was going. Occasionally, it looked as though he affected to call the signals and he could carry the ball all the way alone but he found, obviously, there were areas in this new and enticing field in which he had no place.

Well, concerning what Professor Langenbeck said long years ago, and what has happened since, I think all medical gridirons should be an open field for anyone. The dentist, the person with interests limited to the mouth, the internist, the nutritionist or the surgeon—anyone of these might make contributions to our knowledge of tenors of the mouth, the particular gridiron now under discussion. We need obviously to have more fundamental information about these items. It is unimportant who makes the contribution. He has the knowledge, the interest and tools to explore the field—he becomes the master of the gridiron, no matter by what name they call the field. It is important that all medical fields be open to all interested players.

Can the mouth be used as another index from which to go forward? It certainly is a neglected field by surgeons and I, for one, am happy to have seen these delightful pictures and to know that important work is being done in this area. I wish we knew more about the etiology of some of these diseases than we do.

PSYCHOPHYSIOLOGIC STUDIES IN A FEMALE PATIENT WITH A LARGE GASTRIC FISTULA*†‡

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During the past two and a half years we have been studying a female patient with a large gastric fistula. This lesion was instituted surgically 5 years ago following a complete stenosis of the esophagus after swallowing caustic lye with suicidal intent. Our research methods consisted of psychoanalytic interviews three to five times a week and of physiologic studies three times a week without the participation of the psychoanalyst.

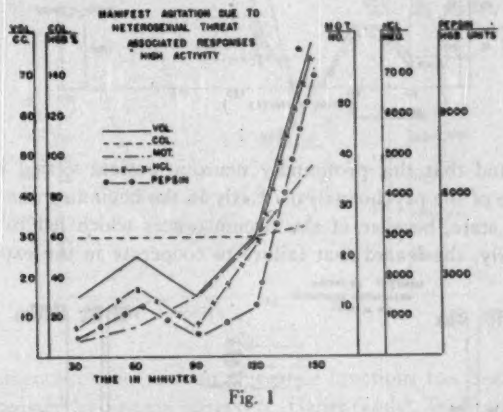

Fig. 1

The physiologist studied the fluctuation of five gastric functions, viz., volume, acidity, pepsin concentration, motility, and vascularity. Standardized physiologic methods were used.

We feel that our psychophysiological research methodology enables us to evaluate the interactions of psychologically unconscious and conscious mental content with the several gastric functions under observation.

It soon became apparent that the physiological observation situation and the manipulations and instrumentation of the physiologist provoked a variety of psy-

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chologic reactions which strongly influenced the gastric responses to physiological and pharmacological stimuli. The psychological unconscious, as observed psychoanalytically, was a potent determinant of apparently spontaneous gastric activity.

The effect of the psychological unconscious is illustrated by a brief review of one segment of our investigation. (An extensive and more detailed report of our observations has been presented elsewhere[1,2].)

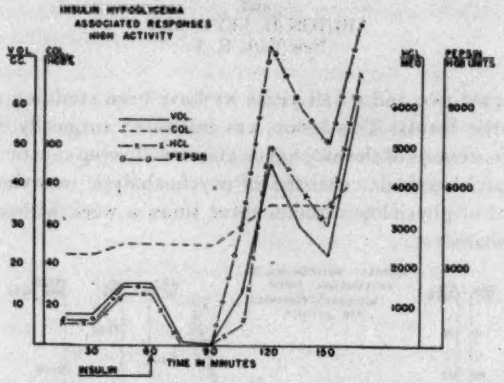

Fig. 2

We had found that this profoundly neurotic patient varied in her behavior during the course of the psychoanalysis. Early in the beginning she was in a guilty, fearful, cringing state, because of the circumstances which led to her suicide attempt. Consciously, she feared that failure to cooperate in the experiments would

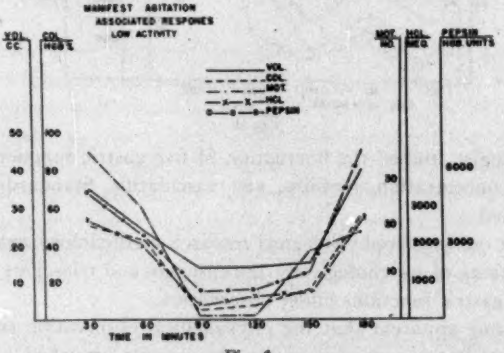

Fig. 3

cause her to be expelled from the hospital which was her refuge and sanctuary. At that time, the physiologic studies demonstrated a synchronous or associated response of her five functions. (See Figures 1, 2 and 3.) They either increased simultaneously or diminished together. This synchronized activity has generally been considered by physiologists to be the usual response to the stimuli employed.

There was one period, however, when the patient seemed happy, relaxed, and went into day-dreams of reveries during the physiologic experiments. During this time the physiologic data revealed a striking change. This was in the nature of an asynchrony or dissociation of the five gastric functions (See Figure 4). The psychoanalyst, working independently of the physiologist, had induced a psychological change by his psychotherapeutic procedure. This preceded the appearance of the dissociation of the five gastric functions. After the patient gained insight through psychoanalytic interpretation into the unconscious significance of her experiences during the experiments, a striking change occurred in her gastric activity. This persisted despite the fact that all the previous experimental conditions remained unchanged, with the exception of the psychological factor. The psychoanalyst was able to predict subsequently when association or dissociation of the gastric functions would occur.

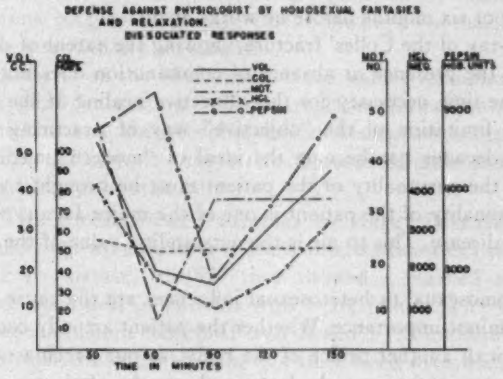

Fig. 4

This phenomenon of dissociation of gastric functions has been commented on without being stressed by several observers. Hellebrandt[3], Wolf and Wolff[4], Davey and Fulton[5], Babkin[6], Schachter[7], among others, have reported it in their protocols.

At present we can only speculate whether this physiological dissociation represents merely random spontaneous fluctuations of the end organ, or, results exclusively from asynchronous impulses from the higher centers, or, from autonomic imbalances due to other factors. We would like, however, to suggest the possibility that frequent and prolonged, or, fixed states of dissociation of gastric functions may play an important pathophysiological role in many functional and organic diseases of the gastrointestinal tract. One such obvious example suggests itself, viz., the dissociation between the motor and secretory disturbances of the stomach in achlorhydric or so-called "gastrogenous" diarrhea. The usual idea that emotional disturbances cause symptoms and disease through severe increase or even decrease of the synchronous functions of an organ may now have to be modified by the phenomenon of dissociation.

Conclusion

1. Organ physiology may be profoundly affected by the psychic reactions of the subject to the experimental situation, the experimenter, and his manipulations.

2. The methodology of the investigation reported demonstrates the potent influence on gastric activity of the psychological unconscious as studied psychoanalytically.

3. Dissociation of the gastric functions, hitherto unemphasized, is presented as a phenomenon which may have significance in health and disease.

Discussion

Dr. I. Snapper:—This excellent piece of research has added to our basic knowledge of gastrointestinal pathology.

We all know that if a man has suffered a Colles' fracture and has no compensation, he will work within one month. If the same patient does have compensation, it may take four or six months before he works again.

Thus the x-ray of the Colles' fracture, showing the extent of dislocation of the fractured parts, the presence or absence of comminution does not give any information about the time necessary for the subjective healing of the Colles' fracture. This shows the limitation of the "objective" way of practicing medicine which during the last decades has become the ideal of "modern" medical teachers. In sound medicine the personality of the patient must be brought to the foreground, because the personality of the patient is one of the major factors which will define the cause of the disease. This to me is the outstanding value of the presentation we have just heard.

Whether homosexual or heterosexual influences are the cause of the ulcer-like symptoms is of minor importance. Whether the patient actually confuses the fistula of the stomach with another orifice of the body, as our psychiatric symbolists assume, may or may not be true. As long as the study of the psychology and the personality of the patient receive due attention next to the laboratory slips which have captivated the sole interest of the physician of today, the experienced clinician will be satisfied.

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THE BIOCHEMICAL APPROACH TO THE TREATMENT OF CHRONIC PROGRESSIVE DISEASES OF NUTRITIONAL ORIGIN

Process Therapy Theory

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"Medical science advances by the logical coordination of facts that may be either old or new. When the logically coordinated application of either old or newly discovered factors is found to fill an existing gap in medical knowledge, it usually becomes evident that some unsolved problem in clinical practise has advanced towards solution."

In this study of the intermediates of tissue carbohydrate and fat metabolism, the endeavor is to present the essentials for a clearer conception of the etiological factors of the chronic progressive diseases due to the impaired mechanisms involved in cell and tissue intermediary metabolism.

Particular stress is on the biochemical blood values as indicators of the biochemical physiological dysfunction, and the resultant clinical pathology. It is proposed to demonstrate how the phosphorylation mechanism holds the key to the factors at fault in the chronic progressive diseases of nutritional origin. (The Process Therapy Theory—Tuttle infra.)

The Biochemical Processes In Heart Disease

Meakins and Long[1] were the first to study intermediates of tissue carbohydrate metabolism in heart disease. In 1927 they showed a marked and proportional increase in blood lactic acid in patients with heart failure. The validity of these results was subsequently both confirmed[2] and denied[3]. The importance of lactic acid as the core of carbohydrate metabolism has since been overshadowed by that of pyruvic acid because of Peters'[4] discovery that the presence of thiamin is necessary for its oxidation.

Taylor, Weiss and Wilkins[5] and later Yanof[6] employed methods of pyruvate blood determinations in subjects with failing hearts. Yanof demonstrated clinically that there is a rise above normal of pyruvic acid in the blood of persons with heart failure. This elevation approximated the degree of failure.

The majority of Weiss and Wilkins' cardiac cases suffering from nutritional deficiency showed the following signs and symptoms: dyspnea on exertion, reduced vital capacity, cardiac and epigastric pulsation, tachycardia, palpitation, gallop rhythm, a bounding peripheral pulse, distended veins and edema. The skin was usually flushed and warm owing to capillary and arteriolar dilation, and the velocity of the peripheral blood flow was increased. Some degree of cardiac enlargement was evident in most cases, but in others, the heart was of normal size. The venous pressure was increased and nearly all cases showed some changes in the electrocardiogram, in which the chief alterations were an inverted T wave and a prolonged QT interval. Examination of the blood showed a rise in the blood sugar and a lowered serum protein.

In studying this series, the patients were placed under observation on a thiamin deficient diet from four to seven days, and then the vitamin was administered intravenously or intramuscularly in doses of 20 to 50 mg. a day. This dosage was purely empirical. Today, as will be outlined later, combinations of the oxytropic factors are more effective. Remarkable improvement was often seen within a few hours, especially in patients with congestive heart failure.

Five cases out of thirty-five in their study died from acute heart failure, but complete recovery from cardiovascular manifestations occurred in the remainder.

The frequency of this form of cardiovascular disease varies with the economic and social level of the population. Weiss[7] noted its occurrence in one of every hundred and sixty medical admissions in a large hospital.

The recognition of cardiac dysfunction remitting from a thiamin hypovitaminosis is based on the following criteria:

A history of nutritional deficiency, either chronic or acute, weakness and fatigue not otherwise accounted for, tachycardia not due to hyperthyroidism, arrhythmia, right-sided enlargement of the heart and increased circulation time; electrocardiographic changes such as an inverted T wave and prolongation of the QT interval; edema not in keeping with the cardiac picture; the state of renal sufficiency and the plasma protein level; all reversed by thiamin therapy.

It has been suggested that the accumulation of metabolites such as pyruvic and lactic acids and methyl glyoxal is a causal factor in the production of the cardiac manifestations of thiamin deficiency. Haynes and Weiss[8] have shown by injecting these metabolites into thiamin deficient animals that this view is incorrect. Their observations support the author's theory that the cardiac manifestations depend on a faulty metabolism, rather than a toxic effect of circulating metabolites.

Govier[9] studied the effect of experimental coronary artery ligation on the coenzyme 1. and cocarboxylase content of the myocardium of the dog. In following his earlier work[10,11] Grieg and Govier demonstrated that the breakdown of intracellular coenzymes occurs in shocks and anoxia, and that the breakdown can be remedied by the administration of the corresponding vitamins. They then investigated another important condition involving tissue anoxia, namely, that of coronary occlusion. When the experiments were begun on coronary ligation, cocarboxylase (diphosphothiamin) was estimated in normal and ischemic cardiac muscle, but nonsignificant changes were demonstrable, contrary to the results obtained in their earlier studies of other tissues in shock[10].

When coenzymes other than cocarboxylase were considered, the fact that the heart muscle is unable to metabolize lactate after coronary occlusion[12] suggested that coenzyme (diphosphopyridine nucleotide), the coenzyme of lactic dehydrogenase, might be destroyed. This is supported by McGinty et al[13] and Bayley et al[14] who demonstrated that lactate is the preferential carbohydrate substrate for heart muscle. A breakdown in its metabolism may be of importance from the standpoint of the viability of the ischemic cells.

The fact that the niacin deficiency produces electrocardiographic changes which are remediable by niacin administration[15], and were strikingly similar to the electro-

cardiographic disturbances reported by Bayley[14] which were produced by coronary artery ligation was further suggestive evidence that anoxia may produce coenzyme breakdown in heart muscle as well as in other tissues.

Govier's experiments resulted in the following conclusions:

1. A consistent breakdown of coenzyme 1. occurred, varying in magnitude from 70 to 83 per cent of normal following coronary ligation and

2. Cocarboxylase was reduced 11 per cent of normal to free thiamin.

Lipmann et al[16], in citing the advances in enzymology and related subjects, established that the easily hydrolyzable phosphorus fraction, particularly adenyl pyrophosphate, plays an important role in the tissue transfer of energy. This compound continuously donates phosphoric acid radicals to the other metabolites and this requires resynthesis continuum. For resynthesis, molecular oxygen is essential. Under anoxia, therefore, the resynthesis would be impaired[17] and hence the content of easily hydrolyzable phosphorus would be diminished. The chain of events resulting from such inhibited resynthesis of easily hydrolyzable phosphorus might contribute considerably to the general pathological consequences of tissue anoxia.

The foregoing conclusions are essential to a better understanding of and are crucial to the postulation of the Process Therapy Theory.

Process Therapy Theory—Tuttle

Intermediary metabolism, in the past, has been largely referred to with little reference to the activators responsible for each of the transformations or to the accumulating knowledge of the characteristic conditions which favor their activity, either as a group or individually. This provides reason for attempting an interpretation of biological energy releases in terms of the enzyme systems as they apply to the problems of the clinician[18].

Our thinking of vitamin deficiencies or intake deficiencies has been revised. A study of the factors which disrupt the normal chain of events in the cell and tissue intermediary metabolism is the more scientific approach to the study of the disease[19].

In all cells, a chemical network of energy distribution is present and is able to carry in the form of special energy, rich phosphate bonds, standard portions of energy. Catabolism consists to a considerable extent of a conversion of potential energy of foodstuffs into directly utilizable phosphate bond energy. Through alternate attachment and release of energy-rich phosphate bonds, catabolism and anabolism are knit together into a largely reversible reaction continuum.

Cellular chemistry involves a harmonious series of consecutive reaction steps which are brought about on a molecular scale by a host of activators, all present in the same reaction fluid. These activators are enzymes and the number and amount of enzymes vary from one cell type to another and determine the individuality of each cell.

Carbohydrate functions in mammalian metabolism not only as an important food but also as an important part of its functioning machinery. In the liver, for example, aside from its use as fuel, it has protective and detoxifying actions and a regulating influence on protein and fat metabolism. All other body tissues con-

stantly require and use carbohydrate under all physiological conditions. Therefore, carbohydrate is an indispensable fuel material and whenever it is not available from food, it is made available by the enzymatic synthesis at the expense of other tissue materials, namely protein or fat[20].

In conditions where metabolic disorders are present, i.e., cardiac disease[6,9], diabetes mellitus[20,30], obesity[31], arthritis[22], chronic progressive deafness[21], cirrhosis, mental diseases[23], etc., carbohydrate metabolism is profoundly disturbed, as evidenced by the blood chemical pathology of hyperpyruvenia or hypercholesterolemia (Table I). The enzyme system's function affects every step of the long and complex chain of carbohydrate synthesis and its utilization. Its impairment is reflected in all the other metabolic steps in these pathological conditions.

Since the breakdown of carbohydrates is essentially similar in all tissue and organs[20] enzyme system deficiency impairs carbohydrate metabolism in every structure of the body. The clinical syndromes that appear are merely the most obvious manifestations occurring in those tissues and organs that suffer most

TABLE I

	Cholesterol	*Pyruvic Acid*
Cardiac disease		
Case 2—male —age 51	309.0	1.79
Case 12—female—age 41	460.0	2.96
Diabetes mellitus		
Case 13—female—age 50	348.0	2.0
Obesity		
Case 1—female—age 59	358.0	3.2
Case 4—male —age 62	396.0	2.9
Arthritis		
Case 11—female—age 45	307.0	2.37
Case 3—female—age 38	289.0	2.38

acutely, and that are most easily accessible to examination. It is a fallacy to regard any single factor of the enzyme systems as more important than another, for the normal chain of events can be broken by lack of any one of them disturbing the normal equilibrium.

To discuss the function of the enzyme systems without reference to nucleic acids is comparable to relating the working of a machine without reference to the motor.

It is well for us to consider the formation of nucleic acid before studying the characteristics of the nucleotides that make up its composition.

Nucleic acid when conjugated with albumin or globulin forms a nucleoprotein. The protein elements may change with the different tissues where the nucleoprotein is formed, but the nucleic acid radicals are relatively constant.

Nucleic acid consists of four nucleotides, two of which are pyrimadines having the nitrogen containing bases thymine and cytosine, and the other two are purines, having the nitrogen containing bases adenine and guanine respectively.

All four nucleotides are basically the same in structure, yet even here in the chemical structure of the nucleus of the cell, we see a normal (balance) equilibrium. That is, the two nucleotides that are pyrimadines are antagonistic to or keep in balance the two purines (Table II).

These balances or equilibriums exist throughout the entire human system, i.e., avidin-biotin, estrogen-androgen, calcium-phosphorus, acetylcholine-choline-esterase, etc. These equilibriums are maintained in the author's estimation by the phosphorylating mechanisms resulting from the adenylic acid system and directly to the nucleic acids. It is *when the phosphorylating mechanism is impaired that pathology arises.*

Clinical evidence[20] discloses that glucose enters the metabolic cycle of the cell by the addition of a phosphate to its end carbon atom. The phosphate is donated by adenosine triphosphate, (the adenylic acid cycle). The adenylic acid cycle occupies a central position in the process and the removal of the inorganic phosphate favors the synthesis of glycogen while the addition of inorganic phosphate hastens the breakdown of glycogen.

The various phosphorylations are the means by which energy liberated from oxidative steps is prevented from being dissipated as heat and is held or built up

TABLE II

NUCLEOTIDE ACTION (ANALYSIS)

Nucleic Acid

Purines	*Pyrimadines*
Adenine nucleotide	*Cytidylic nucleotide*
Guanine nucleotide	*Uridylic nucleotide*

for use. Whereas, the energy of glucose is stored as glycogen, a carbohydrate of higher potential energy, creatine phosphate is in the same relationship to the storage of energy as glycogen is to the storage of carbohydrate. When excesses of energy are being produced over the requirements of the moment, creatine is built up to creatine phosphate for an emergency store to be broken down when energy cannot be supplied as rapidly as required.

SUPPORTING EVIDENCE OF THE THEORY

Biochemical Processes in the Nervous System:—The greatest advance in this field in the last decade has probably been in the elucidation of the phosphorylating mechanism concerned in the metabolism of the brain.

The chief fuel supplying the energy requirements of the brain is glucose. Three different things may happen to the glucose taken up from the blood by the brain: it may be stored as glycogen, glycolyzed and eliminated from the brain as lactate, or oxidized completely to carbon dioxide. In each case the first step is the phosphorylation of glucose to form glucose phosphate.

When cell free tissue extracts or homogenized brain tissue is incubated aerobically with glucose and inorganic phosphate, the glucose, and phosphate disappear, and in the presence of fluoride, phosphorylated products accumulate. These products include fructose diphosphate, phosphoglyceric acid and glucose-6

phosphate, which is believed to be the primary product[24]. Essential components of the system are (a) an oxidizable substrate, such as citrate glutamate or succinate (b) adenylic (c) cozymase and (d) magnesium ions. The adenylic acid acts as a phosphate carrier, while the oxidizable substrate is needed to provide energy for the reaction. Pyruvic acid can serve as an oxidizable substrate provided that a small amount of fumaric acid is also added. In the absence of fluoride, glucose is oxidized by brain dispersions and only small amounts of phosphorylated products accumulate.

The aerobic phosphorylation of glucose is important because it is the primary reaction in the utilization of glucose as a source of energy. The working out of the mechanism of this reaction shows how a phosphorylation may be coupled with an energy producing oxidation reaction, and it illustrates the way in which oxidative energy is utilized in the cell. Cori and Cori[25] have reported the synthesis of glycogen in vitro from glucose-1-phosphate by a purified enzyme phosphorylase from muscle, brain, heart and liver. Adenylic acid is required and the activity of the phosphorylase is increased by the addition of glutathione. The reaction is reversible.

Brain has been considered by many investigators to be a tissue in which non-phosphorylating glycolysis occurs, but Geiger[26] has shown that it has probably a phosphorylating mechanism similar to that in muscle, (the Embden-Meyerhof scheme for muscle). Ochoa[27] found that hexose monophosphate and diphosphate are as readily glycolysed as glucose by cell free preparations of brain. This, too, supports the view that glycolysis in brain proceeds by a phosphorylating mechanism.

A number of investigators have obtained evidence of abnormalities in the carbohydrate metabolism in different types of mental diseases. Lennox, et al[28], measured the oxygen uptake by the brain and the glucose utilization in eighteen patients with petit mal. They found that the ratio of the glucose used to oxygen uptake was 1.08 for the patients with petit mal, and 1.48 for normal individuals. This suggested that the glucose metabolism is abnormal in the brains of patients with petit mal. Abnormalities in the carbohydrate metabolism have also been reported in Mongoloid idiots by Himwich and Frazekas[29].

Biochemical Processes in Diabetes:—Diabetes mellitus is a metabolic disorder, in which carbohydrate metabolism is profoundly disturbed. In every step of the long and complex chains of carbohydrate synthesis or utilization and their reflections in all other myriad metabolic steps, enzyme systems function as the means to accomplish each step[29]. The growing knowledge of the enzyme systems, therefore, has enhanced our understanding of and is crucial to an approach to the treatment of diabetes mellitus.

In terms of organ functioning, the liver is the prime factor for the maintenance of the normal blood sugar level. Once sugar has entered the peripheral tissues, even though it is stored rather than used, it cannot re-enter the blood as glucose, except during periods of relative muscle anoxia, when lactic acid is carried to the liver, converted into glycogen, and reappears as blood sugar (the lactic acid cycle).

Diabetes is considered to be a disease of glucose overproduction, in which there is no diminution of the utilization of blood sugar by the tissues, but the supply of

the sugar to the blood by the liver has become excessive to the point where continued normal utilization can no longer keep pace with it.

The ketone bodies, so frequently associated with diabetes, are normal intermediates of fatty acid catabolism in the liver and they appear in excess in the blood when the hepatic metabolism of fat is sufficiently increased by the lack of carbohydrate substrate mixture. The ketone bodies are readily utilized by peripheral tissues under all known conditions, and ketone bodies and sugar intermediates are competitors for available oxidative mechanisms. Their appearance in the urine is the evidence of the predominance of fat in the competition for available oxygen. Because the liver forms these substances at a much greater rate than it can metabolize them, the liver is practically the sole source of origin for ketone bodies appearing in the urine. Other tissues metabolize them faster than they can produce them. Fatty livers produce much greater amounts of ketone bodies than livers poor in fat.

Not a single hormone has been discovered which has not been shown to exert some influence on carbohydrate metabolism, by virtue of catalytic effects on the enzymatic machinery of metabolism. Insulin is the most effective of all known hormones. With insulin, hypoglycemic effects are invariably obtained, regardless of age, state of nutrition, or the presence or absence of various endocrine glands or visceral organs, and this effect of insulin is a general one and not mediated by any particular organ or tissue. Blood sugar lowering from insulin is primarily the result of the more rapid withdrawal of sugar from the blood by other tissue and secondarily the result of decreased supply of sugar from the liver to the blood.

Insulin is actually a biocatalyst which acts by influencing other biocatalysts. The various physiological effects of insulin which have been described as separate phenomena emerge as merely different parts of the same chain of events. Thus, the fall in the blood sugar level is a direct reflection of the influence of insulin on the basic phosphorylation, and the association of potassium with the hexose phosphates in muscle also accounts for the withdrawal of blood potassium. The accelerated metabolic processes made possible by the increased rate of the first step in the series result in a greater disposal of the substrate both for synthetic and catabolic purposes (i.e., glycogen deposition and R.Q. change).

The increased availability of the substrate of the enzymatic machinery of the cells allows carbohydrate to become predominant over protein and fat in the competition for the oxidative systems. Hence, the catabolism of protein and fat is inhibited (antiketogenesis and nitrogen sparing action). The latter effects are naturally prominent in the liver, which is primarily concerned with the interconversions of foodstuffs while the former effects are more characteristic of the skeletal muscles and the effector organs, which derive their energy chiefly from carbohydrate and ketoacids.

Biochemical Processes in Arthritis:—Arthritis is a systemic disease with joint manifestations. As such, it represents the most disabling condition in the United States and involves approximately one individual of each nineteen of the population.

Arthritis has been etiologically classified as follows:

(1) Rheumatoid or atrophic
(2) Infectional
(3) Degenerative or Hypertrophic
(4) Arthritis of:
    (a) Neuropathic origin
    (b) Neoplastic origin
    (c) Metabolic origin
(5) Traumatic
(6) Miscellaneous

Fifteen years ago in the study of the impaired enzymatic interplay with regard to subjects with arthritis, it was the author's conviction then, as it is now, that in arthritis the enzymes were present in a pattern that resulted in a disturbed purine-pyrimadine equilibrium. This is due to biochemical disturbances which affect the phosphorylation processes involved in the intermediary metabolism, weakening the aerobic processes. It is evidenced by increases in the pyruvic acid levels of the blood.

Pyruvic acid, in excess is a muscle fatigue producing toxin and is probably responsible for the general fatigue associated with the arthritic syndrome.

All biocatalytic substances have an effect on carbohydrate metabolism. In the past two decades, investigators employing biocatalysts in the treatment of arthritis, empirically, have been reporting some amelioration of the symptoms in this condition. The most recent being cortisone and adrenocorticotropic hormone. Since carbohydrate metabolism is essentially the same in all tissues of the body, a disturbance in the long chain of intermediary reactions can produce general systemic conditions.

The disturbed carbohydrate metabolic processes are probably due to climatic trauma, infection, psychosomatic or poor nutritional status.

In the past ten years, a number of methods have been developed to make quantitative measurements of the enzymes concerned with glycolysis and oxidation. Potter[32] in a paper entitled "Cancer As a Problem in Metabolic Pathways", reported: "the Krebs condensation was very weak in homogenates of cancer tissues and this is the reaction by which oxalacetate and acetate are converted to citrate, and is the key reaction in the conversion of pyruvic acid which must be oxidized to acetate".

Evidently, arthritic tissues are unable to oxidize pyruvic acid via acetate to citrate at a rate sufficient to keep pace with pyruvic acid production. As a result of a deficiency in the oxidation processes, the pyruvate, acetate and the oxalacetates are made available for alternate pathways. This may lead to the formation of substances that disrupt normal equilibrium which exists between calcium and phosphorus, purines and pyrimadines, etc. (Refer to the process theory supra.)

The metabolism of pyruvic acid in liver offers an excellent opportunity for the study of several enzymes competing for the same substrate. Pyruvate is oxidized

to an acetate which may pursue two major alternatives; a given molecule of acetate can be used to form either acetoacetates or citrate.

The determining factor must be the phosphorylation mechanism since the normal conjugation of pyruvate is primarily dependent upon the proper functioning of the phosphorylation processes and directly to the nucleic acid.

Summary

Employing the biochemical blood values as indicators of the biochemical dysfunctions associated with pathological conditions, it is endeavored to postulate the Process Therapy Theory as to the etiological factors responsible for the chronic progressive diseases of nutritional origin.

The therapy to follow, predicated on the replacement of the process biocatalysts and the clinical results, bears further evidence substantiating the Process Therapy Theory.

Treatment

Chemotherapeutic agents were prescribed to correct the biochemical dysfunctions. A preparation containing the oxytropic factors of the B-complex group, cocarboxylase (the phosphorylated thiamine), yeast enzymatic hydrolysate and divalent minerals were employed to restore enzymatic interplay and to correct the faulty carbohydrate metabolism. Actually, this combination is the enzyme, diphosphothiamin magnesium protein or carboxylase. Carboxylase serves to catalyze the physiological processes of dehydrogenation and decarboxylation of pyruvic acid in the catabolism of glycogen and indirectly, of lactic acid.

Choline, inositol and methionine were administered to control the lipoid balance in the proper direction, stabilize the colloidal equilibrium of the plasma lipoids, and to reduce the cholesterol levels of the blood.

Dietary restrictions of fats and cholesterol rich foods aided in the reduction of the hypercholesterolemic blood levels.

Thyroid extract was employed to invigorate intracellular oxidation which is an essential measure needed to speed up aerobic and anaerobic oxidation[33].

Lecithin, derived from soya lecithin and sunflower seed oil, is a lipotropic agent used to lower blood cholesterol, because it contains phytesterol which is not utilized in the human economy. The iodine number of these oils is high, therefore, this lipid is correspondingly highly unsaturated. These unsaturated fats lessen the burden on the liver whose function it is to desaturate saturated fats.

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TREATMENT OF HEPATITIS*

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With the discussions on hepatitis which have already been published, a more definite approach to the treatment of this condition is established.

General Precautionary Measures During an Epidemic of Infectious Hepatitis:—Precautionary measures in the case of airborne infections with the entrance through the respiratory tract are limited and follow the general rules. However, even in such epidemics it should be borne in mind that the infecting virus can also be transmitted and spread through fecal contamination and vomited material. The disinfecting measures should follow the rules given for an epidemic of typhoid.

As leakage in the draining system, contaminated wells and other water supplies may be traced as causes of the outbreak of an epidemic, it is advisable that public health officers should be notified and entrusted with investigations. Contaminated canned food certainly may be another source of spread of an infection. If an outbreak occurs in a school, the institution should be closed and a check-up of the families carried out. Although most cases are benign, the turn of an epidemic of hepatitis is incalculable. It may develop into an epidemic of yellow atrophy with a high mortality. The possibility of a long lasting liver damage should be emphasized.

In mass immunizations (measles, mumps, yellow fever, etc.) the use of *pooled* serum and plasma for transfusion purposes should be abolished altogether. The danger of transmitting the hepatitis virus by transfusion considerably increases with the number of donors. The number of serum batches used should be carefully registered and the batch destroyed if an infection can be traced to it. Attempts to sterilize the donor plasma through ultraviolet irradiation have been made by several authors but the results do not warrant confidence in the method. Donors with a history of hepatitis should be excluded.

Individual Care

Prevention of damage and sensitization:—During digestion all sorts of metabolic products—mostly proteinogenic or lipogenic—with potential toxic properties reach the liver through the portal vein. A normal liver with its many detoxicating functions is well able to keep such substances under control. However, there are people whose liver is either constitutionally weak in resistance or has already been damaged by previous attacks and has consequently a lessened resistance and poor function. Such latent liver damage can become manifest in any kind of food-poisoning.

*This is the third in a series on Hepatitis. Upon completion, the entire series will appear in a single reprint.

The term food-poisoning has a very individual connotation and it is common knowledge that food stuffs which are well tolerated by some people are poisonous to others.

It is a problem of the utmost importance and such idiosyncracies have to be considered in all prescriptions for diets. The liver with its varying resistance is undoubtedly in the center of the whole problem. It is a condition for any prevention and protection against further serious liver damage that a latent impairment or a constitutional liver weakness should be discovered at an early stage.

The authors have advocated a screening test of such hepatic inefficiency with the help of the Widal allergic test, and this test is carried out not only with milk but identical results are obtained with other substances to which the individual is allergic. As a rule, patients have a fair knowledge of their liver weaknesses and the fact that they are allergic and have a disturbed liver with certain particular food.

A history of malaria or syphilis and the treatment of these diseases always indicates the possibility of latent liver damage and pregnancy is a well-recognized etiological factor of liver damage.

There are cases where preventive measures should be taken against further damage to the liver which might pave the way for the development of hepatitis. The discovery of a latent liver weakness is important in all cases where the use of drugs known to be potentially toxic to the liver is contemplated. Arsenicals and other heavy metals, mercury, bismuth, gold, sulfanilamides in higher doses and especially on repeated use, barbiturates, cinchophens (atophan) and all sorts of immunizing sera (typhoid, yellow fever, measles, mumps, etc.) may be mentioned. The finding of a latent liver damage should influence the choice of general anesthetic agents.

Antiallergic Treatment:—Adequate and early treatment of the allergic prodromal stage may often successfully prevent the full development of an icteric hepatitis.

The treatment consists of detoxication, magnesium sulfate used orally or by duodenal tube. The importance of taking sufficient doses of magnesium sulfate at the earliest possible time cannot be overrated. It is an emergency measure and can be equally as effective in clearing the liver as a gastric lavage in clearing the stomach after ingestion of poison. Magnesium sulfate not only cleanses the bowels of toxic products but is also effective in initiating a dehydration of fluid from all the tissues toward the bowel and that helps absorb toxic products. It is found to be a strong choleretic. The very first emergency measure cannot usually be applied by the doctor as he is not consulted until the damage has already become apparent, consequently full information and advice about these emergency measures for future incidents must be given to the patient.

Attempts at immunization by anti-virus serum in epidemic hepatitis have been thwarted as the disease has not been successfully transmitted to animals.

Elimination of potential foci infection, tonsils and septic teeth, are particularly important in the lymphatic form of hepatitis. Tonsilectomy has had dramatic success in several instances.

Dehydration Treatment:—Edema of the liver in the case of acute damage is not confined to the interstitial tissue but is observed as intracellular edema as well. It interferes with the blood supply and metabolism and may cause cell degeneration. Early dehydration helps in restoring normal conditions as a most useful therapeutic measure. It is best done with intravenous injections of 20 c.c. of 40-50 per cent glucose solution.

It must be emphasized that this dehydrating measure with hypertonic glucose solutions has nothing to do with the use of glucose as a dietary measure in all liver diseases.

The sudden flooding of the liver with hypertonic solutions causes immediate change in the osmotic and electrostatic potential difference between the cytoplasm and the surrounding fluids and results in dehydration of the edematous cells. As soon as the normal water balance is restored there is no further indication for the administration of hypertonic solutions or for dehydration. Prolonged dehydration may have undesirable effects. The effect of this therapy can be clinically observed by the diminished size of the liver, sometimes even within two hours after injection.

Indications for treatment are present in all cases of liver edema, that is to say, in all inflammatory processes, also conditions of stasis and congestion. Forty c.c. of a 50 per cent glucose solution should be given daily for a period not exceeding four or five days. Apart from this nonspecific effect of general dehydration following intravenous injection, there is a specific effect on cell metabolism. Not only are there carbohydrates restored as glycogen in the liver, but the liver restores bilirubin although not in a microscopically visible form, stores of lipoids and also proteins. All sorts of foreign substances which are excreted by the bile do not pass directly through the liver cell but are retained for some time to be released and excreted gradually.

A dye, tetraiodphenolphthalein, injected intravenously disappears from the blood within 30 to 40 minutes. The x-ray outline of the gallbladder, on the other hand, appears as a rule only after 14 hours and reaches a maximum density around the 16th hour. Where is the dye in the meantime? The generally accepted answer is that the dye is excreted with the bile and present in the gallbladder within an hour after the injection but that it is in a dilution below x-ray visibility. During the subsequent hours, the dye-containing bile is concentrated in the bladder five to eight times until after about 15 hours full x-ray density is reached. No doubt this process of concentration takes place and the x-ray density tends to increase hourly. However, this explanation covers only one part of what actually happens. This can be proved by a simple additional experiment.

When, following the injection of dye, 20 c.c. of a 50 per cent glucose solution is injected, the galibladder gives a shadow of sufficient density as early as two hours

after injection. This observation obviously challenges the correctness of the conception that the concentration time of the bile fully explains the delay of x-ray visibility.

The experiment can be elaborated by injecting glucose at different intervals after the dye. The shadow appears regularly one to two hours after the glucose injection. That is to say, when a large amount of glucose is suddenly offered to the liver cell, it *cleans the other stored products to make space for the increase in its glycogen.*

Our observations suggest that a sudden offer of concentrated glucose solution induces the liver to dispose of other stored products of normal metabolism like bile pigments, lipids, etc. The glycogen storing function apparently is one of the strongest vital functions of the liver cell.

Bed Rest:—Indications for bed rest are as follows. They have been confirmed and have proved their value by the clinical experience of almost all observers.

1. Any exertion is followed by undue fatigue and increased edematous enlargement of the liver. Too early rising in the convalescent stage has frequently caused relapse.

2. Appearances of hemorrhagic phenomena even in early stages are incalculable. The danger is increased by physical exertion.

3. Central nervous system signs may appear unexpectedly. We don't mobilize the patient until the serum bilirubin level drops to almost normal.

Diet:—The old rules for diet in hepatitis: high carbohydrates, low fat diet, still stand unchallenged. However, the whole question has been re-examined and discussed in recent times through discovery of the value of a high-protein diet. Moreover, the importance of diet has been brought into the limelight through experiments showing that defective diet in animals may produce fatty infiltration of the liver, slowly developing into cirrhosis in some instances and may lead to acute necrosis in others.

Carbohydrate diet:—There is hardly any argument about the value and necessity of an abundant supply of carbohydrates in all cases of hepatitis and hepatic insufficiency. Complex carbohydrates in the form of starch are given as mashed potatoes, rice, porridge of all kinds. To all these basic carbohydrate meals almost unlimited amounts of glucose can be mixed with fruit juice; stewed and mashed raw fruits are usually well tolerated. Raw vegetables as carrots, celery, spinach leaves, beet roots mixed with green salad and bananas can be given freely. Artichokes and asparagus have a certain choleretic effect.

Glucose Therapy:—This occupies a special place within the framework of a high carbohydrate diet. Glucose, as the simplest representative of the CHO group, can be rightly compared with highly combustible fuel in relation to heavy fuel of the complex carbohydrates in our daily bread and potatoes. Glucose incites other metabolic processes and the old saying that fat burns only in the fire of carbohydrates is an expression of this fact. The experience that glucose considerably shortens the time of the so-called "second wind" in the case of muscular exercise is another proof of the special value of this simple carbohydrate.

As far back as 1924, small doses of insulin (8-10 units) in addition to glucose have been recommended as aiding glycogen storage.

While there has been some questioning of the value of insulin, the authors cannot agree with the opinion that the administration of 8 or 10 units of insulin in addition to the glucose has anything but a most valuable aid in liver storage. Numerous clinical cases treated with insulin demonstrated unquestionably and impressively its aid.

Protein Diet (amino acids and lipotropics):—Up to recent times the generally accepted rule was to give a low protein diet in all cases of hepatic damage. The advice was based on the following considerations. It was feared that a damaged liver might fail in its important work of protein metabolism and that an incomplete and abnormal breakdown would lead to the appearance of toxic proteinogenic amines. This conception was supported by experiments on dogs, in which by an Eck-fistula, the portal blood was diverted directly into the inferior vena cava thus excluding the liver. The animals showed decreased tolerance for proteins and in many instances died of "meat intoxication". Meat and meat extracts have proved positively harmful to animals in which experimental liver damage was inflicted through poisoning with carbon tetrachloride. Extrarenal azotemia and uremia were observed to be caused by hepatic insufficiency.

Other experiments:—On the other hand, there are other experiments which proved the importance of proteins for protection of the liver cells. Only in recent times has more attention been paid to the clinical significance of hypoproteinemia in hepatitis.

Leaving apart the fact that a state of hypoproteinemia lessens the general resistance of the patients to shock, anesthesia, intoxications of all kinds, and lessens the facilities for wound healing and all cell regeneration, this state has apparently a special significance in hepatitis. The albumin-fraction of the serum proteins drops in the initial stages of hepatitis, when albumin and fluid diffuses through the damaged cell and capillary walls, and thus the normal A/G balance is disturbed.

It was definitely established that lack of proteins in starving animals rendered the liver more susceptible to damage and that proteins, like carbohydrates, could also protect the liver of dogs against chloroform poisoning (Whipple et al—1919). A protein meal before anesthesia is beneficial.

The explanation of these controversial experiments and clinical observations was soon found by analysis of the effect of the different amino acids and polypeptides. Certain amino acids containing a labile sulfhydryl group or a methyl group were responsible for preventing liver cell damage. Methionine, which contains both groups, is probably the key-substance and an indispensable amino acid.

However, it was demonstrated (Whipple et al) that the time factor plays an important role in producing this liver cell protection. When administered shortly before chloroform narcosis, methionine gives complete protection. Three to four hours after anesthesia there is only partial protection, and no protection at all was observed when more than four hours had elapsed.

Clinical application:—The influence of the most valuable contribution of experimental medicine to the question of protein diet and the action of lipotropics has been seen in the fact that the rigid low-protein diet in hepatitis has been abandoned by most clinicians. High carbohydrate diet was combined with a reasonably high protein diet. However, many authors emphasize the importance of high caloric value as the main principle. The beneficial effect of a high caloric diet, rich not only in carbohydrates but also in proteins, has been established by many authors especially for the chronic forms of hepatitis (cirrhosis) (Patek et al, A. R. Rich and Hamilton, W. H. Barker, Watson et al). The dietary regimen as recommended by Patek, Parker, etc., may be mentioned. Three thousand daily calories are distributed in the following proportions:

Protein	139 gm.
Carbohydrates	365 gm.
Fat	175 gm.

The diet consists of: meat, milk, eggs, fruit, green vegetables, and the meat is served twice daily, the milk five times daily.

Vitamins: 25 gm. powdered brewer's yeast is served in milk twice daily in increasing amounts. If powdered yeast is badly tolerated liquid yeast is given and in addition, 5 mg. thiamine hydrochloride is given intramuscularly. Concentrated liver extract is given twice a week. Fluids are given up to 2,000 c.c. daily. Methionine or cystine plus choline is given in daily injections.

With a broader study of hepatitis the use of the single substance choline in 15 gram doses 3 to 6 times a day appears to be beneficial according to the opinion of some observers.

It should be generally accepted that only fresh butter or pure olive oil should be given with a fair amount of Vitamin B-complex. Folic acid, if available, may be given in addition.

Protein (200 grams) can be given in dried skimmed milk powder which can be added to soup, potatoes, and fruit juices. Lean meat (calf, chicken, fish) is given in moderate quantities. There is no limit to the intake of carbohydrates. The amount should be as high as possible. (Glucose, fruit juices, honey, cereals, mashed potatoes, stewed fruits). Vegetables can be given in the form of tomatoes, lettuce, spinach, mashed carrots. Amongst fruit, bananas and fresh grapes stand in first place. Strictly forbidden are all fried foods or fats, except butter and olive oil, and alcohol even in the smallest quantities.

Summarizing the results reported up to now, it must be admitted that the therapeutic results of choline and methionine did not live up to the high expectations suggested by the results of experimental medicine.

Parenteral nourishment with protein hydrolysates, glucose and vitamins, has proven highly beneficial in such cases. While in cirrhosis there is hardly any danger in over-feeding and excellent effects of the high caloric diet have been confirmed, more caution is necessary in acute hepatitis.

The term "high protein diet" is too general and rather misleading. The term should read "high caloric and selected protein amino acid diet". While the old

rules of a high carbohydrate and fat-less, or at least low fat diet, remain unchallenged, a fair amount of protein added to the diet is distinctly helpful but some of the darker meats containing high creatinin content are definitely harmful in hepatic damage. The dry milk products on the other hand are probably useful.

Fat Digestion in Hepatitis (The Action of Cholecysmon)

Tolerance for fat is greatly diminished in almost all cases of hepatitis, whether associated with jaundice or not. In jaundiced cases this decreased tolerance can well be understood through the lack of bile with its activators for the pancreatic lipases (bile salts, cholecysmon) which are an essential help for fat absorption and digestion.

However, in nonjaundiced cases of hepatitis also, intolerance for fat can be such that intake of a fat may cause serious relapse. In hepatitis, fat is as seriously toxic to the liver as alcohol, arsenicals, etc. The authors have devoted much time and work to studying this interesting question with the help of a very experienced cook.

The following facts were established in a long series of experiments. Butter and olive oil, provided they are absolutely fresh and pure, can best be tolerated even by jaundiced patients. Peanut butter and combined artificial products sometimes cause bad reactions in the form of indigestion, flatulence, anorexia, nausea and even vomiting. Recurrence of jaundice in convalescent patients has been observed. An interesting observation is that while warm, freshly liquefied butter is well tolerated, it causes indigestion when allowed to cool off or is consumed in a rewarmed state. Clear rules for diet result from these experiments and conform with all the old precepts.

The authors have been able to establish a scale of *fat digestibility* which corresponds roughly with practical experience. This shows that the most digestible fats are olive oil and butter, the less digestible are lard and other animal fats and combined "artificial" fats.

It has been proved that the fat-splitting action of lipase is probably independent of the actual amount of ferment present and at least does not increase in proportion to the latter. This fact, amongst others, illustrates the importance of the activating substances, the strongest of which, cholecysmon, has been discovered in the wall of the gallbladder and is a constant product of secretion in a normal organ. Cholecysmon has been tested clinically for its value in improving the tolerance for fatty food in cases of hepatitis and for replacing certain functions of a destroyed or removed gallbladder.

The Principle of Liver Cell Gymnastics

Since the experimental work of Forsgren, we know that the liver cell works with a special rhythm and that the different metabolic functions are not only separated in time but apparently take place in different zones of the liver cell. On the other hand, there is a distribution of different functions within one liver lobule (Geraudel-Elton). Every liver unit, probably every liver cell, has a certain store of different metabolic products, that is to say, there are not only carbo-

hydrate stores in the form of glycogen but also stores of bile pigments—although normally not in a microscopically visible form—and probably also protein stores. Foreign substances given orally or intravenously are removed from the blood and stored within the liver cell for a considerable period and are only gradually and rhythmically released and excreted with the bile.

Forsgren and his co-workers found that between the two phases of assimilation and dissimilation or secretion, the actual size of the liver and its weight undergoes considerable changes. Forsgren insists that this *intrinsic* functional rhythm exists independently of the intake of food. It is a rhythmic function of the liver cells.

This rhythmic action of the liver cells can be likened to muscular development in which the putting of a muscle on tension will not strengthen the muscle but only be introducing rhythmical change between tension and relaxation. The liver cell function develops under much the same principle. This we have been pleased to designate as liver cell gymnastics. With an ample supply of glucose, we are in a position to favor and reinforce the assimilatory phase and by the administration of thyroxin were able to stimulate the dissimilatory phase, it having been established that thyroxin is an agent capable of depleting the storage of various substances in the liver cells.

The scheme of treatment is as follows: After a general "cell cleaning" by intravenous injection of 50 per cent glucose solution on two days, the actual liver cell gymnastics start. Two days of high glucose supply, stimulating the assimilatory phases of the liver cells, are followed by two days free of all carbohydrates when injections of thyroxin are given, a substance which stimulates the dissimilatory phases and the depletion of the glycogen stores. We have added on the glucose days, eight units of insulin.

Forsgren maintains that the intrinsic rhythm of the liver cells is so strong that it can hardly be influenced either by food intake or by the state of sleep and wakefulness. The course of the curves he obtained was independent of meals. Apparently sleep exerts no regular influence either, because a trough taking place in the early evening might already have begun in the afternoon, several hours before the subject went to sleep and may be followed by a rise in the later half of the night during sleep. In contrast with these observations, the influence on the liver cell activity was established beyond any doubt in our experiments. By means of continuous curves we determined the bilirubin and blood sugar content of the blood serum. We obtained very definite rhythmic curves which may be considered as more or less the expression of the liver cell gymnastics.

The functional liver cell gymnastics are by no means confined to carbohydrate metabolism. They also influence in an analogous way, bilirubin, cholesterol and urea metabolism. The insulin days represent the assimilatory days of storage, whereas on the thyroxin days the cell is squeezed out, so to speak, and the products of metabolism are absorbed into the blood stream. The peaks of the curves correspond to the depletion of glycogen stores, to the squeez-

ing out of the cell on the thyroxin days; the troughs correspond to the insulin days of storage.

The scheme for liver cell gymnastics described above is, of course, only one way of influencing the rhythmical activity of the liver cells. We have tried other ways and many others may still be found. We have substituted extracts of adrenal cortex for thyroxin. We have exercised another rhythm by a scheme of two days full diet alternated with two days of complete fasting, continued for six weeks. Injections of hypertonic solutions were followed by injections of distilled water. The influence of all these rhythmic schemes on the metabolism is indeed remarkable and we believe the conception merits further clinical investigation.

Calcium Therapy:—Calcium therapy in the treatment of hepatitis is not very popular. The author, however, is satisfied with the great value of intravenous injections of calcium gluconate, which are given two to three times weekly together with Vitamin C. The theoretical basis is disputed and the explanation of its effect is not yet quite clear. The calcium ion certainly has some antiallergic properties, it tightens the capillary walls and in this way combats edema and inflammation. It prevents perhaps also the pathological "transmineralization" of the damaged liver cells where, according to Keller-Eppinger, emigration of calcium ions from the cells take place. L. J. Witts explains the calcium effect as a neutralization of guanidine and other products of incomplete metabolism or liver autolysis. Whatever the biological facts may be, according to practical experience in the wards a wider use of calcium gluconate injections in the treatment of hepatitis is recommended.

Choleretics:—Choleretics, that is to say substances which are known to increase the secretion of bile, have for a long time had their place in the treatment of hepatitis. Bile salts or bile acids rank amongst the strongest for this purpose, decholin (dehydro-cholic acid) being the most popular. F. F. Boyce has recently recommended warmly the use of decholin in hepatitis, especially in the post-operative course.

It is interesting to note in this connection that H. Schwiegk found that intravenous injection of as little as 10 c.c. of decholin nearly doubled the pressure in the hepatic artery, but produced only a small pressure rise in the portal system. He concludes that the first result of an injection of decholin is a hyperemia of the liver, associated with increased oxygen supply. The result is increased choleresis of the liver cells. Moreover, increased blood supply to the liver cells is certainly highly useful for recuperation and regeneration.

Decholin is reported to have some value also in the treatment of the hepato-renal syndromes arising from hepatic insufficiency (F. F. Boyce). The favorable effect of bile salts is perhaps due to an improvement of glycine synthesis in the damaged liver. However, it should be mentioned that intravenous injections of decholin are badly tolerated by many patients. There are many other choleretics on the market.

The authors are not satisfied that hepatitis is strikingly improved by the use of the above-mentioned choleretics. They cannot recall one case of severe hepatitis

where the excretory block in the liver cells could actually be broken by the use of choleretics like decholin. Unfavorable side-effects, such as nausea, vomiting, etc., are, on the other hand, very frequent. Of all choleretics 50 per cent glucose solution by intravenous injection has proved to be by far the best. Small doses of decholin can be added without harm and perhaps increase the effect.

Diathermy:—Diathermy has been tried out very frequently with the idea of increasing choleresis in the expectation of reproducing the favorable effect of diuresis on excretory disturbances of the kidney. However, the effect on choleresis is not entirely convincing. Nevertheless, diathermy has a favorable effect by frequently bringing relief to the patient where there is epigastric or hypochondriac pressure. It has, however, to be borne in mind that diathermy is strictly contraindicated—like all applications of warmth—in all cases of acute inflammation of the gallbladder.

Liver Extract:—Injections of liver extract have a favorable effect in the phases of reconstruction and cell regeneration and are indicated in all cases of anemia.

Blood Transfusion:—Little can be found in the literature about any special value for blood transfusion in hepatitis. Indications for it are certainly given by many of the complications such as anemia, or hemorrhage from portal hypertension. Venesection with removal of 500 c.c. followed by blood transfusion had a favorable effect in one case of subacute atrophy observed by the authors.

Vitamins:—There is some deficiency in storage and metabolism of practically all vitamins in hepatic insufficiency. Ample supply of vitamins therefore is beneficial and can do no harm. Definite indications for Vitamin K or its substitutes are given as soon as a hemorrhagic tendency appears. Vitamin A is required in cirrhosis when signs of night blindness appear. Vitamin B-complex seems to have a good effect in protection and regeneration of the liver cell as well as in depleting fat stores which interfere with the cell metabolism. Vitamin C acts as a kind of catalyst in stimulating metabolic processes and cell regeneration. Vitamin D plays its role in maintaining the important calcium level in the blood and tissues.

Treatment of Complications

Cholemia and Hepatic Coma:—The conditions leading to a comatose state in the course of an acute or chronic hepatitis are complicated and cannot be explained simply by the term "cholemia" and a sudden breakdown of hepatic function. The intimate connection between affections of the liver and the central nervous system should be remembered. In some cases of acute infective hepatitis such nervous symptoms appear in the very early stages of the disease.

Hepatic coma further cannot be simply explained by the disappearence of glycogen and the loss of the liver's function of storing this important substance. In cases where mechanical obstruction of the duct system has led to hepatic insufficiency there is generally no striking lack of glycogen in the liver cells.

Particularly of value are the intravenous injections of the B Vitamins and the particular preparation, because of its facility of use, of Berocca C.

The intravenous use of plasma is lifesaving in several cases. The use of aureomycin intravenously has a particular value in the acute inflammatory type, perhaps in preventing complicating cholangitis by increasing reports coming in that in hepatic cirrhosis it seems to produce a state simulating a reversal, which up to this period has been simply periods of quiescence with a return of their former symptoms after a period of time which in many cases again were able to be arrested.

The use of Cortone, while still in the experimental stages, in guarded doses, would appear to have a favorable effect.

Surgical treatment of Hepatojaundice (Relief of the excretory block):—The surgical approach to the pathology of hepatojaundice is based on some interesting observations made and reported by numerous authors including ourselves when operating on such cases with the erroneous diagnosis of an obstructive jaundice. The observation was that although no obstruction in the common duct was found, bile drainage, which had completely stopped for weeks and months started sometimes dramatically upon opening the common duct at operation. No surgical credit could be claimed for this fortunate happening as no obstruction had been removed. Nevertheless this sudden and unexplained onset of bile drainage following opening or mere manipulating of the common duct formed a turning point in the course of the disease. A remarkable number of patients, some of them considered almost lost, recovered quickly with the disappearance of jaundice. Schlegel in 1926 quoted a collection of 41 cases of hepatojaundice, mainly acute atrophy of the liver, in whom operation was performed. Out of 26 cases with common duct drainage 17 were benefited. Frangenheim in 1929 reported that 10 out of 11 were cured by operation. Our personal observations cover a series of 12 cases of hepatitis, which, without any signs of improvement clinically gave the impression of an approaching coma. In some of them the presence of a malignancy was suspected. The results were as follows: 3 patients died in hepatic coma within the next days without relief. One patient recovered dramatically with jaundice having almost disappeared within one week. He died however in a shock following blood transfusion. Eight patients recovered completely with bile drainage having set in on the operating table or within 24 hours postoperatively.

The following is the record of a patient, a man of 46 with a history of jaundice of 8 weeks. The clinical diagnosis was carcinoma of the head of the pancreas or of the papilla. At operation, the extrahepatic ducts were found to be free of any obstruction and contained whitish bile. The liver was yellowish green and flabby. The gallbladder was distended and contained thick concentrated bile. About 20 minutes after the opening of the common duct, secretion of yellowish bile set in on the operating table. Common duct drainage was established and the patient recovered quickly.

V. Haberer reported on a case of a 32-year old woman in whom, in the course of an antiluetic treatment, grave hepatojaundice developed leading to hepatic coma. Cholecystostomy was performed and the patient recovered rapidly with lasting results contrary to all expectations.

The previous conception that the drainage of the gallbladder or of the common duct relieved the stasis and presumed back pressure cannot be sustained. All observations point against this conception. There is hardly any increased pressure in the duct. The papilla is free. When the gallbladder was found to be distended and contained concentrated bile, it was not through back pressure. Enlargement of the gallbladder was of the atonic paralytic type. The wall of the gallbladder was sometimes found to be flabby in spite of the distention and the gallbladder could be emptied easily by finger pressure.

The whole state of the extrahepatic duct system is in most cases that of paralysis as explained in the chapter on hepatitis. The most striking observation was a rapid onset of bile drainage after opening the gallbladder or the common duct or even after simple manipulations of the gallbladder and the bile duct. This can only be explained by assuming that the excretory block is relieved by some change in nervous regulation.

Benecke and Backhaus think that toxins cause a spasm in the arterioles supplying the liver lobules and thus interfere with the proper blood supply of the cells, which is the actual reason for cell damage and necrosis. The authors saw improvement after simple exposure and exploration of the bile ducts. The favorable effect on the liver is, according to their opinion, caused by spasmolysis and consequent hyperemia in the liver lobules.

Whatever the actual detailed mechanism is, the effect of the operation must be due to the manipulations on the sympathetic nerves around the common duct and the gallbladder. This concept finds support in the fact that a similar effect of releasing the excretory block in the liver can be obtained by paravertebral (epidural) injection of novocaine solution between D11-D12 (W. Dick).

Removal of toxic products from the liver through drainage might also have, in some cases, a favorable influence on the toxic paralysis of the extrahepatic system. In the case of secondary ascending infection of the bile ducts, the favorable effect of drainage can be easily understood. The drain might further have a certain stimulating effect on the secretion through suction and hyperemia.

Interesting observations have been reported by Caroli. He examined the bile draining out immediately after operation in a case of icteric hepatitis, and stated that with an increasing amount of bile pigment a considerable amount of sodium chlorate and albumin was discharged, suggesting that inflammatory effusion from the Disse spaces was also draining through the bile duct. We must conclude that there is a communication between the Disse spaces and the bile capillaries in their ampullar part. This author found in the first three tests on the draining bile:

9.7 gr.		3.50
9.3 gr.	sodium chlorate and	3.30 albumin
9.50 gr.		1.32

Three or four days later the values dropped to:

2.34 2.57	sodium chlorate and only	0.50 albumin

Choice of Cholecystostomy or Choledochostomy:—The following rules for the choice of operation seem to be quite well founded: In serious cases of hepatitis with clinical signs of a threatening hepatic coma, i.e., central nervous system symptoms, the simplest operation involving the least risk, that is cholecystostomy, should be performed. Good results can be expected especially in cases where the gallbladder is found distended.

The patient may recover quickly after this operation, which is best performed under spinal anesthesia. Repeated washout of the gallbladder with warm saline solution stimulates bile drainage and can be recommended. Cholecystoduodenostomy has proved satisfactory in three cases of Rost.

However, if the general state of the patient permits, *common duct drainage* is preferable. This holds true especially where there is a complicating cholangitis as indicated by a spiking temperature. On microscopical examination of biopsy specimens, hepatic cholangitis is quite frequently found and is probably due to an ascending infection, favored by the paralysis of the biliary ducts.

Sterility of the gallbladder bile does not mean that the common duct bile is sterile as well. We found in one case that the gallbladder bile was sterile while from the common duct B. Coli were grown. A similar case was reported by V. Haberer who performed cholecystostomy for hepatic jaundice. The gallbladder bile was found to be sterile, but chills and spiking temperatures in the history indicated a cholangitis. As the symptoms persisted, drainage of the common duct was performed four weeks later. Bile from the common duct contained B. Coli.

It is interesting and worth mentioning that such an intrahepatic cholangitis with round cell infiltration around the bile capillaries, and even real cholangic abscesses, may completely heal within a very short time after drainage of the common duct. In a case of Frangenheim a piece of liver had been excised at operation for drainage and showed intrahepatic cholangitis. Five years later laparotomy was done for repair of an incisional hernia. Again a piece of liver was examined and was found to be perfectly normal. One of us (P.) has seen similar cases. The period of drainage should be at least four to six weeks. A definite disadvantage of cholecystostomy is that the fistula sometimes does not close and another operation is required.

Sympathetic Block (Epidural Anesthesia)

Technic:—Thirty to forty c.c. of 1.5 per cent novocain (procain) solution is injected epidurally between D11 and D12. Injections are repeated after two to three days interval. This simple method is worth trying before the major operation is decided on. W. Dick reported 14 cases in which epidural anesthesia provoked an almost immediate onset of bile secretion and rapid improvement.

One of us (P.) has had a dramatic effect in one case of a patient in a precomatose state where operation was already decided on. However, a trial with paravertebral block was made before. Forty c.c. of 1½ per cent novocaine solution was injected actually between D10-D12. Twenty-four hours later the stool was

bile stained for the first time in six weeks and the patient recovered. In other cases, however, no success could be obtained.

Indications:—In the opinion of the writers, indication is given for surgery when in the case of hepatic jaundice it is dragging on and some clinical symptoms such as increased sleepiness or restlessness may signal a danger for a turn into hepatic coma and liver atrophy. Thorough preoperative treatment with Vitamin K is important.

AN EVALUATION OF THE ANTACID ACTIVITY OF A "SPECIAL" ALUMINUM HYDROXIDE MIXTURE

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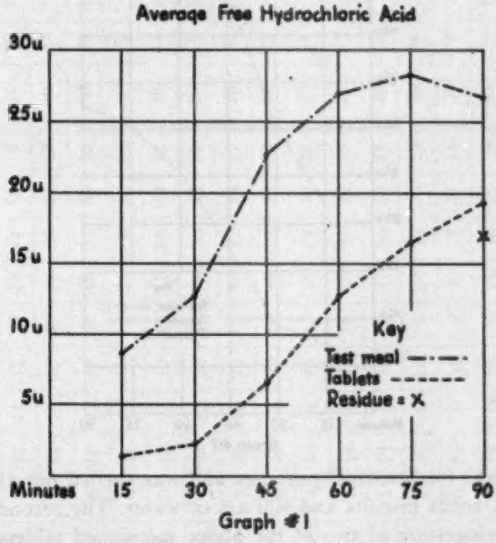
The etiology of peptic ulcer has not been definitely established. However, it is generally accepted that the free hydrochloric acid secreted by the acid-bearing cells, if it is not the actual cause, at least facilitates the development of peptic ulcers. Consequently, all medically accepted treatments for this disease are, to a large measure, directed towards elimination and/or control of this acid factor.



Graph #1

The antacid powders employed in the Sippy routine have a rebound effect with a resultant hyperacidity[1]. This secretagogue reaction likewise develops with the use of protein hydrolysate[2]. It has been demonstrated that N.N.R. aluminum hydroxide gel, being of the reactive variety[3], is constipating[4]. Besides having the least untoward effects, the most desirable antacid would naturally be one producing the most prolonged neutralization of the free hydrochloric acid.

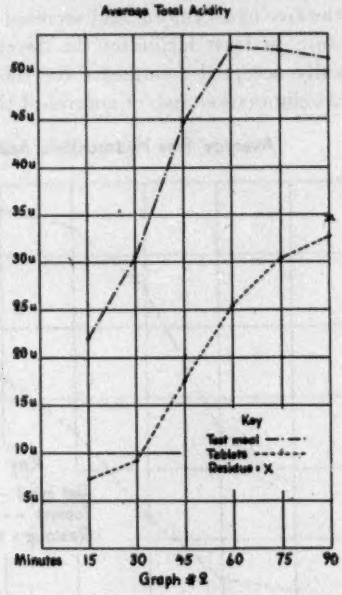
The study herein reported was for the purpose of determining the duration of the neutralizing property of a preparation of which each tablet contained 2¼ grains "special" aluminum hydroxide, 1 1/10 grains calcium carbonate, 1⅓ grains magne-

sium peroxide, 3/40 grain phosphate salt of 3-diethylamino-2, 2-dimethyl-propanol tropic acid ester and oil of peppermint as a flavoring agent*.

Method

Twenty ambulatory patients with gastrointestinal symptoms, but not necessarily with gastroduodenal disease, were used in this study. Every effort was made to standardize the conditions under which the patients were studied to avoid extrinsic or intrinsic factors that could influence the acid secretion[5,6].

A gastric residue study was carried out on each patient. Subsequently, a study was conducted on each patient on two consecutive days. The patients reported each day at 9 A. M. without having ingested anything, not even water, for nine hours.



Graph # 2

The first study was for "control" purposes and was carried out after the ingestion of six unsalted Uneeda biscuits and 400 c.c. of water. The second study was conducted after the ingestion of two of the above mentioned tablets and 400 c.c. of water. Each study consisted of fractional gastric analysis every fifteen minutes starting from the time of ingestion of the biscuits or tablets and was concluded at the ninety minute period. No reported[7] difficulties were encountered in obtaining specimens after the sixty minute period, but suction for extraction was carried out slowly and gently and in some instances the Levin tube had to be partly withdrawn or lowered into the stomach.

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*The medicament used in this study was obtained through the courtesy of Hoffmann-La Roche Inc., Nutley, New Jersey and is manufactured under the trade-name Syntrogel®. The authors take this opportunity to express their appreciation for this grant.

TABLE I

Case	Diag.	Free Hydrochloric Acid Res.	15 min.		30 min.		45 min.		60 min.		75 min.		90 min.	
			E	S	E	S	E	S	E	S	E	S	E	S
1	U	8	4	0	8	0	12	8	22	14	20	30	20	24
2	V	24	8	0	8	0	18	2	36	12	36	20	30	22
3	W	20	8	4	10	2	20	14	22	20	18	12	18	2
4	W	4	14	4	16	10	24	18	40	30	34	38	20	32
5	W	32	10	4	14	8	38	22	36	38	38	32	34	46
6	U	8	10	0	16	0	28	2	32	2	30	6	28	18
7	W	8	4	0	6	0	12	8	20	14	22	16	18	12
8	W	28	4	0	8	4	24	10	22	18	32	16	38	30
9	Y	14	6	0	10	6	28	18	20	16	18	12	16	12
10	Y	20	10	0	20	0	24	8	28	14	30	22	20	20
11	W	12	8	0	10	0	16	4	20	12	28	14	28	18
12	X	16	6	0	10	2	18	8	24	14	28	14	28	16
13	Y	20	16	0	20	2	30	8	34	10	32	16	36	18
14	Y	10	8	0	14	0	20	0	18	4	28	10	30	12
15	X	16	0	0	10	0	24	0	32	8	30	14	32	18
16	Z	20	20	2	22	4	28	0	20	0	14	6	10	6
17	Y	40	18	8	25	4	38	2	42	14	42	16	44	22
18	U	0	0	0	0	0	0	0	6	0	12	0	12	0
19	V	10	10	0	12	0	24	2	30	8	34	18	32	22
20	W	30	8	4	16	0	28	0	36	10	40	22	44	36

Case	Total Acidity Res.	15 min.		30 min.		45 min.		60 min.		75 min.		90 min.	
		E	S	E	S	E	S	E	S	E	S	E	S
1	38	12	6	20	10	22	10	42	24	42	50	36	44
2	48	20	4	22	4	40	8	66	28	64	34	62	40
3	40	20	12	26	10	50	40	54	38	50	20	46	14
4	20	24	12	28	16	36	34	62	52	40	60	36	48
5	50	28	10	34	14	58	46	54	50	58	44	56	58
6	20	30	8	42	10	58	14	58	16	46	20	40	32
7	20	16	6	20	10	28	18	42	30	40	30	34	20
8	46	16	10	28	14	52	30	50	38	52	36	68	50
9	26	20	8	22	14	40	32	38	28	38	30	36	28
10	42	28	10	44	14	52	20	54	30	60	38	44	32
11	28	14	4	26	6	38	8	42	20	50	28	52	34
12	34	16	4	28	8	40	20	52	24	60	28	58	26
13	38	34	6	36	8	52	20	52	20	50	28	50	30
14	20	24	2	28	2	42	6	42	12	54	16	56	20
15	30	8	0	26	4	58	8	70	20	66	32	66	40
16	42	34	10	48	18	56	10	52	14	40	20	32	24
17	62	36	14	50	8	68	8	74	20	70	26	72	36
18	8	6	2	8	2	10	2	28	2	40	2	42	2
19	28	26	2	30	2	42	8	50	16	50	24	60	30
20	54	28	16	44	10	52	14	70	30	72	42	80	50

Key: Diag.—Diagnosis Res.—Residue E—Test meal S—Tablets U—Biliary tract pathology V—Diverticulum of duodenum
W—Peptic ulcer X—Peptic ulcer symptom complex Y—Gastrointestinal neurosis Z—Gastric carcinoma

The extracted specimens were filtered through four layers of gauze. An analysis for free hydrochloric acid and total acidity was carried out in the usual manner using Toepfer's reagent and phenolphthalein as indicators and N/10 sodium hydroxide for titration.

Observations

Table I reveals that case #18 had no free hydrochloric acid in the gastric residue although fractional aspiration was continued for 45 minutes after the meal and for 90 minutes after the tablets. Case #15 was completely neutralized only up to 15 minutes after the meal and for 45 minutes after the tablets. None of the other cases were at any time completely neutralized after the meal. Subsequent to the ingestion

TABLE II

Average Acidity

Time	Test Meal	Tablets
	Average Free Hydrochloric Acid	
15 min.	8.6	1.3
30 min.	12.75	2.1
45 min.	22.7	6.7
60 min.	27	12.9
75 min.	28.3	16.7
90 min.	26.9	19.3
	Average Total Acidity	
15 min.	22	7.3
30 min.	30.5	9.2
45 min.	44.7	17.8
60 min.	52.6	25.6
75 min.	52.1	30.4
90 min.	51.3	32.9

of the two tablets in 14 cases, the free hydrochloric acid was completely neutralized at 15 minutes, 11 at 30 minutes, 5 at 45 minutes and 2 at 60 minutes.

Accepting 15 units of free hydrochloric acid as an average normal, Table II reveals that the meal reduced the acid below normal for only 30 minutes. The tablets maintained a below average normal for one hour. Further, accepting 30 units for the total acidity as an average normal, this was reached at 30 minutes after the meal and 75 minutes after the tablets.

The average gastric residue figures of this series was 17 units of free hydrochloric acid and 34.7 units for the total acidity. A rise above each of these figures developed 45 minutes after the meal. Only a slight elevation above the free hydro-

chloric acid average developed at 90 minutes with no elevation of the total acidity subsequent to ingestion of the tablets.

Conclusions

In this series of twenty cases the tablets reduced the average gastric residue free hydrochloric acid up to the 75 minute period. At 90 minutes there was a slight rebound of 2.3 units. At no time during the study did the total acidity return to the average gastric residue figure.

A control study with a bland meal revealed that a rebound of free hydrochloric acid developed at 45 minutes and the total acidity surpassed the average gastric residue by ten units at the same period.

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INCARCERATED APPENDIX IN A STRANGULATED FEMORAL HERNIA

Review of Literature and Case Report

DAVID ROSE, M.D., F.A.C.S.*
Boston, Mass.

The occurrence of incarcerated appendix in a femoral hernia is relatively uncommon. A review of the literature reveals four cases. In 1908, Crispin[1] reported a case of a 75-year old woman in whom repair of an incarcerated femoral hernia revealed the sac to contain the vermiform appendix and intestines. Morris[2] in 1909, reported one case. This case involved a 36-year old woman in whom a gangrenous tip of an appendix was found in a femoral sac. The finding of the appendix in the sac was not suspected, as the patient was afebrile, and the diagnosis was that of incarcerated femoral hernia. Downes[3] reported a 28-year old woman who was operated upon for a strangulated femoral hernia: the sac containing only the appendix. Knapp[4] in 1944 reported a 63-year old male who was operated upon with a diagnosis of incarcerated femoral hernia. The hernial sac was found to contain the appendix and the mesoappendix.

In all the above cases, there were no febrile reactions and little or no nausea or vomiting preoperatively. In all of the cases, the diagnosis was incarcerated femoral hernia and the presence of the appendix in the hernial sac was unsuspected. It is also of interest to note that of the four cases quoted, three occurred in females. In the case which we are reporting, the same pattern was followed. It occurred in a female, was not associated with febrile reaction and had only minor nausea and vomiting, and the presence of the appendix in the hernia was not suspected. In all cases, recovery without complication occurred.

Case Report

Miss E. M. B., U-57285, a 63-year old white woman, was admitted to the Wyman House of the Mount Auburn Hospital by her attending physician, Dr. Leo A. Blacklow, on May 30, 1948, and we saw her in consultation shortly after admission.

This patient gave the history of vague abdominal pain and distress for more than a year. In July, 1947, she had been admitted to the Mount Auburn Hospital for cardiac failure. At that time, her diagnosis was rheumatic heart disease, auricular fibrillation, and cardiac decompensation with left-sided heart failure. She responded to treatment and was discharged with normal heart rhythm and full compensation. She remained well and continued at her employment as a saleswoman until her present admission.

At 2 A.M. on the day of admission, she was awakened by severe, persistent abdominal cramps, associated with pain in the lower abdomen. She vomited once

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and then fell asleep from "sheer exhaustion". Upon awakening later in the morning, she noted that a "lump" in the right groin was tender to the touch and moderately painful. There was no further vomiting, but the cramps returned and became progressively worse. After several hours had elapsed without relief, she called her local physician and was admitted to the hospital.

Physical Examination revealed a thin, frail, white female. The neck veins were slightly distended. Heart—Apical impulse was just outside the midclavicular line. There was a palpable thrill. Rhythm was slow, 60-62, and irregular. There was no pulse deficit. There was a soft, systolic murmur at the apex, transmitted over the precordium. Lungs—Clear. Abdomen—Liver palpable two fingers below the costal margin. There was soft, intestinal distention. Both lower quadrants were slightly tender, without spasm, rigidity or rebound tenderness. The right groin was the site of a soft swelling, which extended partially below Poupart's ligament. This swelling was tender, tense, and fixed. The skin was not reddened. The mass measured about 4 cm. x 2.5 cm. Extremities—Normal. Rectal and vaginal examinations—Negative. Blood pressure on admission: 180/80; Temperature: 98.

Laboratory Data—Blood—R.B.C., 4,100,000; W.B.C., 16,400; Hb., 15.6 gms; 9 stabs, 62 segs, 27 lymphs, 2 monos. Urine—yellow, cloudy, acid; specific gravity —1.025; no albumin, sugar, or acetone; few bacteria. A diagnosis of strangulated femoral hernia was made, and operation performed.

Operation—Under spinal anesthesia an incision was made parallel to Poupart's ligament, with the mesial end carried down over the pubic bone, and through the aponeurosis of the external oblique. The transversalis fascia was divided, exposing the peritoneum. The lower margin of the skin and fascia were retracted and the mass revealed. The mass was blue, lobulated and seemed cystic. The peritoneum was then opened and the right lower pelvis explored. No visible aperture was found. The cecum was found lying free in the right pelvis and a small section of the appendix seemed to be adherent to the lower peritoneum close to the pubis. Gentle traction on the appendix found it to be firmly fixed. Dissection of the mass proved it to be definitely cystic, filled with a thin, bloody fluid. When the fluid was evacuated, the hernial sac was isolated and when opened, disclosed the appendix; swollen, black and firmly fixed. Poupart's ligament was divided down to the appendix, thus releasing the constriction. The appendix was then removed in the usual manner. The hernial sac and remnants of cystic structure were then removed proximal to Poupart's ligament, and the peritoneum closed. Poupart's ligament was sutured and repair of the femoral hernia effected in the usual manner. The patient's condition at the conclusion of operation was good. An uneventful recovery followed and the patient was discharged on June 7, 1948, in good condition.

Pathological Report:—(Dr. H. Edward MacMahon)*

Gross Description:—The specimen consists of an appendix, measuring 8 x 1 cm. The serosal surface in the distal third is black in color, covered by a layer of grayish-white fibrin. The wall is thickened and in the distal third, there is hem-

*Pathologist, Mount Auburn Hospital, Cambridge, Mass.

orrhage into the wall. Also received is a small sac measuring 4.5 cm. in length. There is a sac within the sac in the superior portion. The smaller sac is firmly attached to the membranous tissue covering it.

Microscopic Diagnosis:—Healed appendicitis with obliteration of the tip, and scarring of the wall, acute hemorrhagic infarction (venous) involving the distal one-third of the appendix, complicated by a very recent acute inflammatory reaction such as one sees as a complication of venous infarction.

Section of the hernial sac shows a very recent fibrinous inflammatory reaction with degeneration necrosis and desquamation of lining serosal cells and with the deposition of fibrin, red blood cells and scattered leucocytes over the surface. The wall itself shows a low-grade chronic inflammatory reaction with fibrosis of the wall, lymphocytic infiltration and serosal cyst formation consistent with earlier and healed inflammatory reactions. Another interesting feature of the wall of the hernia is the presence of compact nests of lymphocytes throughout the adjacent fat tissue.

The overall picture is one of a hernial sac showing recurrent inflammation and of an appendix showing venous infarction superimposed on earlier inflammatory reactions.

Summary

Review of the literature discloses four reported cases of appendix incarcerated in a femoral hernia. The above cited case brings the total of reported cases to five. Of these five cases, four occurred in females. All were afebrile at onset and had either slight or no nausea and vomiting.

A case of incarcerated appendix in a strangulated femoral hernia with a serosal cyst of the hernial sac is reported. The appendix revealed hemorrhagic infarction.

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NEWS NOTES

Meeting of the Executive Committee

A meeting of the Executive Committee of the National Gastroenterological Association was held in New York City on Sunday, 21 January 1951.

In addition to routine administrative matters the Secretary-General, Dr. Roy Upham, reported on the meetings of the New York, New Jersey and Wilkes-Barre-Scranton Chapters.

The Memphis, New Jersey and New York Chapters presented for ratification the applications of the following, which applications were approved by them and accepted by the Executive Committee as indicated: Dr. C. H. Porter, Memphis, Tenn., Member; Dr. Richard A. Hopping, Newark, N. J., Member; Dr. Chas. B. Ripstein, Brooklyn, N. Y., Member; Dr. Jacob Melnick, Brooklyn, N. Y., Member; Dr. Aaron S. Werner, Brooklyn, N. Y., Member.

The following were elected to membership-at-large in the National Gastroenterological Association: Dr. James H. Goode, Tuscaloosa, Ala., Member; Dr. Bruce C. Lockwood, Detroit, Mich., Fellow; Dr. Samuel L. Governale, Chicago, Ill., Member; Dr. Sidney Davidson, Lake Worth, Fla., Fellow; Dr. Daniel E. Earley, Cincinnati, Ohio, Fellow; and Dr. Harold L. Joslyn, St. Louis, Mo., Member.

Upon presentation of the necessary qualifications, the following were advanced as indicated: Dr. S. William Kalb, Newark, N. J., Associate Fellow; Dr. J. B. Michaud, Drummondville, Canada, Associate Fellow and Dr. Samuel S. Feuerstein, Long Island City, N. Y., Associate Fellow.

Estimated budgets for the Association and The Review of Gastroenterology were submitted and adopted for the year 1951.

Dr. Tidmarsh reported that the Program Committee had visited Chicago and made plans to present a scientific program for the convention, consisting of several symposia.

Life Fellowship fees were set as follows: from the age 40-50, $500.00; from 50-60, $300.00 and from age 60-70, $100.00.

The date for the Semi-annual meeting of the National Council was set for 1 April 1951 in New York City.

At the meeting of the Executive Committee held in New York City on 1 April 1951 Dr. Roy Upham, Secretary-General reported that the Rhode Island, New York and New Jersey Chapters had held meetings.

Dr. William W. Lermann, President-elect reported that he had visited the West Coast Chapters in San Francisco, Los Angeles and Santa Barbara. The group there was enthusiastic about future meetings and were interested in the National Association holding an Annual Convention on the West Coast.

The Editor, Dr. Samuel Weiss presented a financial statement for The Review of Gastroenterology.

The Treasurer, Dr. Elihu Katz submitted a financial statement which was accepted.

The question of the 1953 convention was discussed and New Orleans, Los Angeles and San Francisco considered as meeting places.

The Exhibit Manager, Mr. Steven K. Herlitz, submitted a request to the committee that future exhibits at conventions be limited to those firms who would have something of technical interest to present and who further would agree to have representatives of their research departments available at the convention. This was approved.

At the meeting of the Executive Committee held in New York City on Sunday, 20 May 1951 Dr. Roy Upham reported on the meetings of the New Jersey, Boston and Milwaukee Chapters.

Dr. Upham told the committee that he and the Executive Officer, Mr. Weiss had attended a meeting of the Grand Rapids Chapter in Grand Rapids and had visited Cleveland for the purpose of organizing the Cleveland Chapter.

The question of a meeting place for 1953 was again discussed and referred back to the committee for further information.

With the consent of the Executive Committee, the President, Dr. Tidmarsh, appointed the following to the Nominating Committee: Dr. William W. Lermann, Pittsburgh, Pa., Chairman; Dr. Chas. W. McClure, Boston, Mass.; Dr. E. A. Marshall, Cleveland, Ohio; Dr. G. Randolph Manning, New York, N. Y. and Dr. C. J. Tidmarsh, Montreal, Canada.

Members of the committe will serve for a period of 3 years and present nominations for Fellows to be elected to the National Council and as officers of the Association.

The Boston, Grand Rapids, New Jersey, New York and Philadelphia Chapters presented for ratification the applications for membership of the following, which applications were approved by them and accepted by the Executive Board: Dr. Marcio M. Bueno, Fall River, Mass., Member; Dr. Benjamin R. Van Zwalenburg, Grand Rapids, Mich., Fellow; Dr. Kenneth H. Judy, Fort George G. Meade, Md., Member; Dr. Louis E. Zimmer, Newark, N. J., Member; Dr. Richard J. Lempke, Jersey City, N. J., Member; Dr. Solomon Resnick, Jersey City, N. J., Member; Dr. Israel N. Schenker, Jersey City, N. J., Member; Dr. Ralph D. Eichhorn, New York, N. Y., Member; Dr. Alvin D. Yasuna, Bronx, N. Y., Member and Dr. Philip Fieman, Philadelphia, Pa., Member.

Dr. Abraham H. Barris, Long Beach, N. Y., was elected to membership-at-large in the National Gastroenterological Association.

Upon presentation of the necessary qualifications, the following were advanced as indicated: Dr. Walter J. Schacht, Milwaukee, Wisc., Associate Fellow; Dr. Thomas G. Wilkinson, Pittsburgh, Pa., Associate Fellow; Dr. Stanley Moleski, Grand Rapids, Mich., Associate Fellow; Dr. Emil Schwarzmann, New York, N. Y., Fellow; Dr. Arthur A. Kirchner, Los Angeles, Calif., Fellow; Dr. Esther Tuttle, New York, N. Y., Associate Fellow; Dr. Thad. A. Krolicki, Providence, R. I., Fellow; Dr. T. F. Nelson, Tampa, Fla., Associate Fellow; Dr. A. G. Lavoie, Springfield, Mass., Fellow; Dr. M. E. Steinberg, Portland, Ore., Fellow; Dr. Sidney

Messer, Los Angeles, Calif., Associate Fellow; Dr. Samuel A. Robins, Boston, Mass., Associate Fellow; Dr. John N. Dill, Yonkers, N. Y., Associate Fellow; Dr. Lester Crismon, Aruba, N.W.I., Associate Fellow; Dr. Edward F. Sciorsci, Hoboken, N. J., Associate Fellow; Dr. Edward J. Krol, Chicago, Ill., Associate Fellow; Dr. John D. Yeagley, York, Pa., Associate Fellow; Dr. Max Gratz, Miami Beach, Fla., Associate Fellow; Dr. Emil L. Santangelo, Paterson, N. J., Associate Fellow; Dr. Reginald B. Weiler, Pueblo, Colo., Associate Fellow; Dr. Irvin Sussman, Bridgeton, N. J., Associate Fellow; Dr. Jordan Propatoridis, Athens, Greece, Associate Fellow; Dr. D. W. Creek, Santa Barbara, Calif., Associate Fellow; Dr. Emile Gribovsky, Huntington, West Va., Associate Fellow; Dr. Samuel H. Rubin, Asbury Park, N. J., Associate Fellow; Dr. Benjamin Kogut, Brooklyn, N. Y., Associate Fellow; Dr. Henry B. Steinbach, Detroit, Mich., Associate Fellow; Dr. John J. Byrne, Boston, Mass., Fellow; Dr. Edward Levy, New York, N. Y., Fellow.

Course in Postgraduate Gastroenterology

The National Gastroenterological Association announces that its course in Postgraduate Gastroenterology will be given at The Drake in Chicago, Illinois on September 20, 21, 22, 1951.

This year the course will again be under the direction and co-chairmanship of Dr. Owen H. Wangensteen, Professor of Surgery of the University of Minnesota Medical School, who will serve as surgical co-ordinator and Dr. I Snapper, Director of Medical Education of The Mt. Sinai Hospital, N. Y., N. Y., who will serve as medical co-ordinator.

Drs. Wangensteen and Snapper will be assisted by a distinguished faculty selected from the medical schools in and around Chicago whose presentations will cover the following subjects: diseases of the mouth, diseases of the esophagus, peptic ulcer, diseases of the stomach, diseases of the pancreas, cholecystic disease, psychosomatic aspects of gastrointestinal disease, diseases of the liver, diseases of the colon and rectum, and other miscellaneous subjects including pathology and physiology, radiology, gastroscopy, etc.

For further information and enrollment write to the National Gastroenterological Association, Department GSR, 1819 Broadway, New York 23, New York.

In Memoriam

We record with profound sorrow the untimely passing of Dr. Jean A. Le Sage, Fellow, Montreal, Canada and Dr. Herbert L. Weinberger, Fellow, New Orleans, La.

Our deepest sympathies to the bereaved families.

IN COMING ISSUES

Papers presented before the 15th Annual Convention of the National Gastroenterological Association and before the Course in Postgraduate Gastroenterology.

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$$\frac{dx}{dC} = K(S-x)$$

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It's *simply* physical

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$$K - \frac{dx}{dc} = \frac{S-x}{x^n}$$

$$\frac{S}{S-x} - Ax = KC$$

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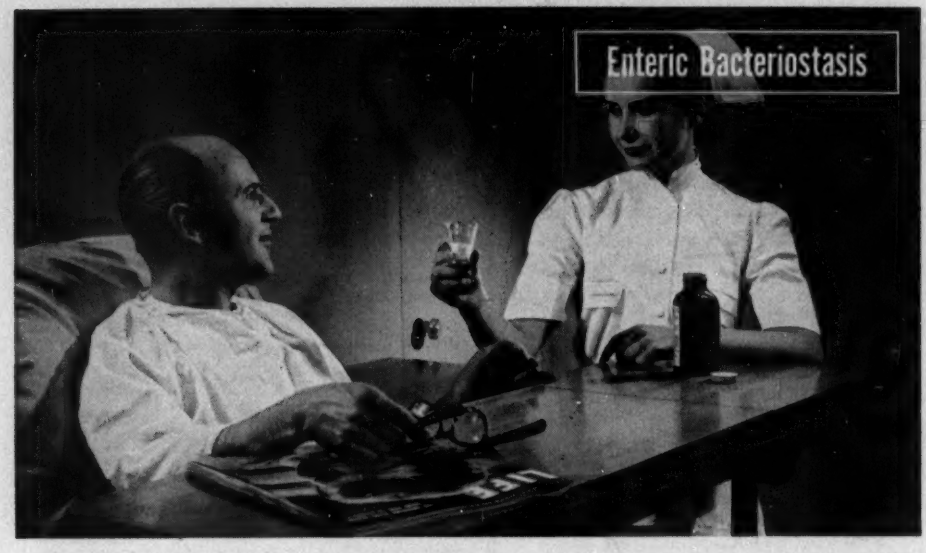

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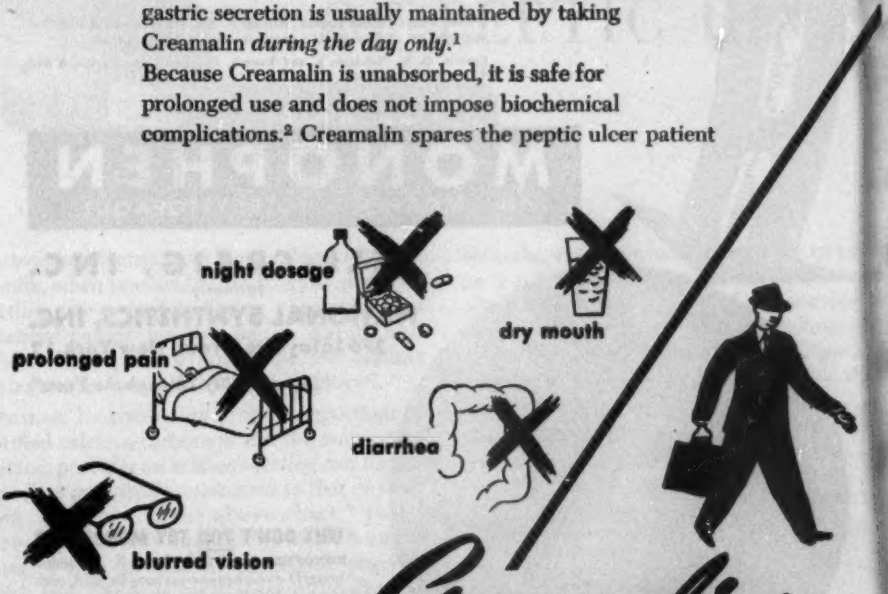

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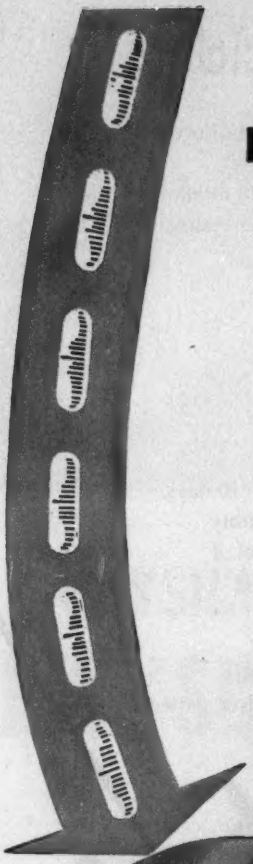
1. Breuhaus, H. C., Akre, O. H., and Eyerly, J. B.: *Gastroenterology,* 16:72, Sept., 1950.
2. Jordan, Sara M.: *Ann. West. Med. & Surg.,* 4:133, Mar., 1950.



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Epstein, B. S., Natelson, S. and Kramer, B.: Am. J. Roentgenol. & Rad. Ther., 56:201-207, 1946

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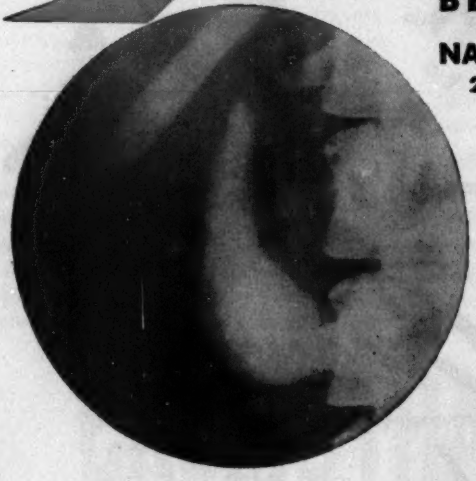

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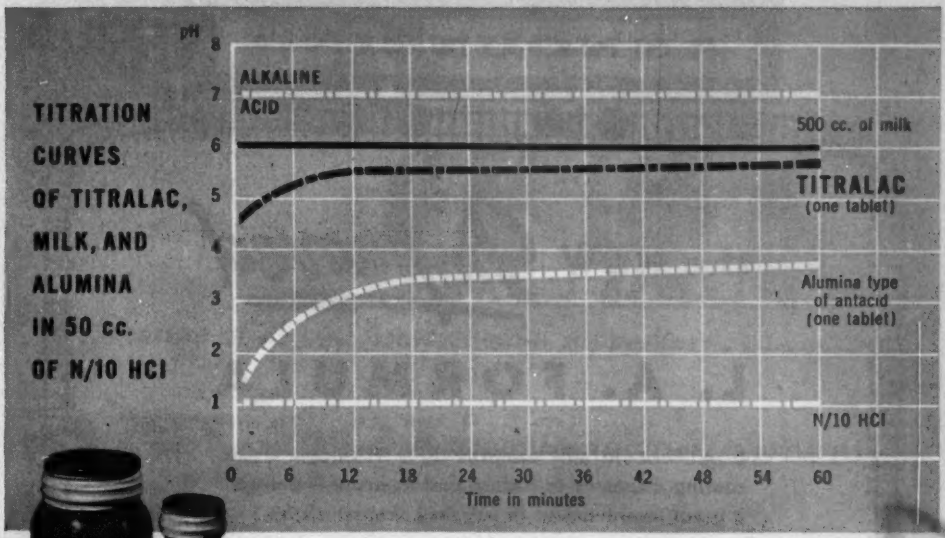

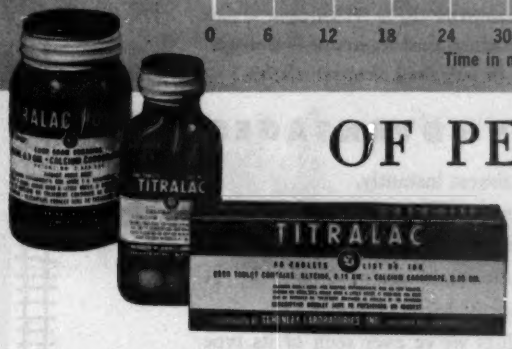

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REFERENCES

1. Rossett, N. E., and Flexner, J.: Ann. Int. Med. 18: 193 (1944). 2. Freezer, C. R. E.; Gibson, C. S., and Matthews, E.: Guy's Hosp. Reports 78: 191 (1928). 3. Aaron, A. H.; Lipp, W. F., and Milch, E.: J. A. M. A. 139: 514 (Feb. 19) 1949. 4. Kirsner, J. B., and Palmer, W. L.: Illinois M. J. 94: 357 (Dec.) 1948. 5. Kimball, S.: in Practice of Medicine (Tice). Hagerstown, Md., W. F. Prior Company, Inc. 1948; p. 210. 6. Special Article: M. Times 76: 10 (Jan.) 1948.

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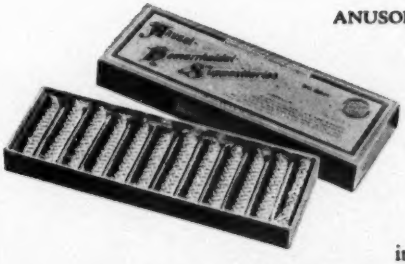

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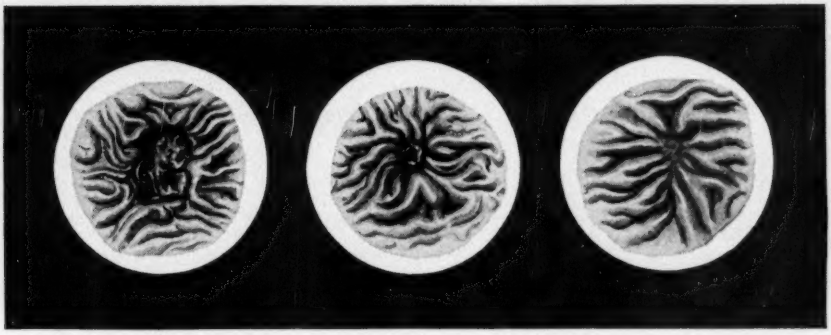

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